A METHOD FOR THE TREATMENT, PREVENTION, OR INHIBITION OF A CNS DISORDER AND/OR PAIN AND INFLAMMATION USING A COMBINATION OF DULOXETINE, VENLAFAXINE OR ATOMOXETINE AND A CYCLOOXYGENASE-2 SELECTIVE INHIBITOR AND COMPOSITIONS THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

This Application claims priority from U.S. Provisional Application Serial No. 60/433,790 filed December 17, 2002.

BACKGROUND OF THE INVENTION

(1) Field of the Invention:

The present invention relates to methods for the treatment, prevention, or inhibition of a central nervous system (CNS) disorder pain (*e.g.*, neuropathic pain), and/or pain and inflammation and compositions for such treatment. The present invention is directed more particularly to methods for the treatment, prevention, or inhibition of a CNS disorder and/or pain (*e.g.*, neuropathic pain) and inflammation in subjects needing such treatment, prevention, or inhibition and to compositions comprising duloxetine, venlafaxine or atomoxetine and a cyclooxygenase-2 selective inhibitor that are useful in such methods.

(2) Description of Related Art:

Inflammation is a manifestation of the body's response to tissue damage and infection. Although the complex mechanisms of inflammation are not fully elucidated, inflammation is known to have a close relationship with the immune response and to be associated with pain and fever in the subject.

Prostaglandins are known to be important mediators of inflammation, as well as to regulate other significant, non-inflammation-related, functions. Regulation of the production and activity of

prostaglandins has been a common target of antiinflammatory drug discovery activities. However, common non-steroidal antiinflammatory drugs (NSAIDs) that are active in reducing the prostaglandin-induced pain and swelling associated with the inflammation process also have an effect, sometimes adverse, upon other prostaglandin-regulated processes not associated with the inflammation process. The use of high doses of many common NSAIDs can produce severe side effects that limit their therapeutic potential.

The mechanism ascribed to many of the common NSAIDs is the modulation of prostaglandin synthesis by inhibition of cyclooxygenases that catalyze the transformation of arachidonic acid -- the first step in the prostaglandin synthesis pathway. It has recently been discovered that two cyclooxygenases are involved in this transformation. These enzymes have been termed cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). See, Needleman, P. *et al., J. Rheumatol., 24, Suppl.49*:6 - 8 (1997). See, Fu, J. Y., *et al., J. Biol. Chem., 265(28)*:16737-40 (1990).

COX-1 has been shown to be a constitutively produced enzyme that is involved in many of the non-inflammatory regulatory functions associated with prostaglandins. COX-2, on the other hand, is an inducible enzyme having significant involvement in the inflammatory process. Inflammation causes the induction of COX-2, leading to the release of prostanoids, which sensitize peripheral nociceptor terminals and produce localized pain hypersensitivity. See, *e.g.,* Samad, T. A. *et al., Nature, 410(6827)*:471-5 (2001). Many of the common NSAIDs are now known to be inhibitors of both COX-1 and COX-2. Accordingly, when administered in sufficiently high levels, these NSAIDs affect not only the inflammatory consequences of COX-2 activity, but also the beneficial activities of COX-1.

Recently, compounds that selectively inhibit cyclooxygenase-2 have been discovered. These compounds selectively inhibit the activity of

COX-2 to a much greater extent than the activity of COX-1. The new COX-2-selective inhibitors are believed to offer advantages that include the capacity to prevent or reduce inflammation while avoiding harmful side effects associated with the inhibition of COX-1. Thus, cyclooxygenase-2-selective inhibitors have shown great promise for use in therapies -- especially those which require extended administration, such as for pain and inflammation control for arthritis. Additional information on the identification of cyclooxygenase-2-selective inhibitors can be found in references such as: (1) Buttgereit, F. *et al., Am. J. Med., 110(3 Suppl. 1)*:13-9 (2001); (2) Osiri, M. *et al, Arthritis Care Res., 12(5)*:351-62 (1999); (3) Buttar, N.S. *et al., Mayo Clin. Proc., 75(10)*:1027-38 (2000); (4) Wollheim, F. A., *Current Opin. Rheumatol., 13:*193-201 (2001); (5) U.S. Patent Nos. 5,434,178 (1,3,5-trisubstituted pyrazole compounds); (6) 5,476,944 (derivatives of cyclic phenolic thioethers); (7) 5,643,933 (substituted sulfonylphenylheterocycles); 5,859,257 (isoxazole compounds); (8) 5,932,598 (prodrugs of benzenesulfonamide-containing COX-2 inhibitors); (9) 6,156,781 (substituted pyrazolyl benzenesulfonamides); (10) 6,110,960 (for dihydrobenzopyran and related compounds), and (11) 6,180,651 (includes disclosure of BMS-347070).

The identity, efficacy and side effects of new cyclooxygenase-2-selective inhibitors for the treatment of inflammation have been reported. References include: (1) Hillson, J. L. *et al., Expert Opin. Pharmacother., 1(5)*:1053-66 (2000), (for rofecoxib, Vioxx®, Merck & Co., Inc.); (2) Everts, B. *et al., Clin. Rheumatol., 19(5)*:331-43 (2000), (for celecoxib, Celebrex®, Pharmacia Corporation, and rofecoxib); (3) Jamali, F., *J. Pharm. Pharm. Sci., 4(1)*:1 - 6 (2001), (for celecoxib); (4) U.S. Patent Nos. 5,521,207 and 5,760,068 (for substituted pyrazolyl benzenesulfonamides); (5) Davies, N. M. *et al., Clinical Genetics*, Abstr. at http://www.mmhc.com/cg/articles/CG0006/davies.html (for meloxicam, celecoxib, valdecoxib, parecoxib, deracoxib, and rofecoxib); (6)

http://www.celebrex.com (for celecoxib); (7) http://www.docguide.com/dg.nsf/PrintPrint/F1F8DDD2D8B0094085256 98F00742187, 5/9/2001 (for etoricoxib, MK-663, Merck & Co., Inc.); (8) Saag, K. *et al., Arch. Fam. Med., 9(10)*:1124 - 34 (2000), (for rofecoxib); (9) International Patent Publication No. WO 00/24719 (for ABT 963, Abbott Laboratories).

Published U.S. Patent Application No. 2001/0029257 A1 (published on October 11, 2001; hereinafter "Murdock") discloses the topical use of various anti-inflammatory drugs in combination with amine containing compounds as a muscle relaxant or as an analgesic to relieve pain (see abstract). However, Murdock is limited to transdermally applied compositions. Example 10 of Murdock discloses the formation of a gel containing venlafaxine and soya lecithin. According to Example 29 of Murdock, the venlafaxine/soya lecithin gel is to be applied to the skin for at least one (1) hour. Murdock does not, however, disclose specific compositions comprising duloxetine, venlafaxine or atomoxetine and a COX-2 selective inhibitor or any use thereof, specifically their use for the relief of a CNS disorder, pain (*e.g.*, including neuropathic pain) and/or inflammation.

Even though the treatment and prevention of pain and inflammation, such as is caused by a CNS disorder, arthritis and other inflammation-associated disorders, has advanced very significantly during the past several years, there still remains a need for improved methods and compositions that prevent and/or treat pain and inflammation, and particularly for methods and compositions that are efficacious for such applications in physiologically acceptable dosages, and which are selective in their physiological impact.

SUMMARY OF THE INVENTION

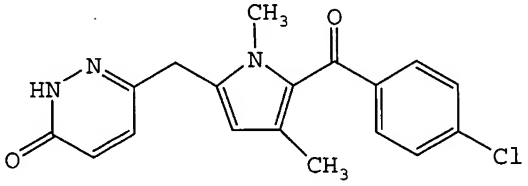
Briefly, therefore the invention is directed to a novel method for the treatment, prevention, or inhibition of a CNS disorder and/or pain (*e.g.*,

neuropathic pain) and inflammation or an inflammation-associated disorder in a subject in need of such treatment, prevention, or inhibition, comprising administering duloxetine, venlafaxine or atomoxetine (or combinations thereof) and a cyclooxygenase-2 selective inhibitor or prodrug thereof to the subject.

According to another embodiment, it is to be understood that any other NRI may be substituted for the duloxetine, venlafaxine or atomoxetine (or combinations thereof) in connection with any one or more embodiments of the invention disclosed herein.

The invention is also directed to a novel composition comprising duloxetine, venlafaxine or atomoxetine (or combinations thereof) and a COX-2 inhibitor or prodrug thereof for the treatment, prevention, or inhibition of a CNS disorder and/or pain (*e.g.*, neuropathic pain) and inflammation, or an inflammation-associated disorder.

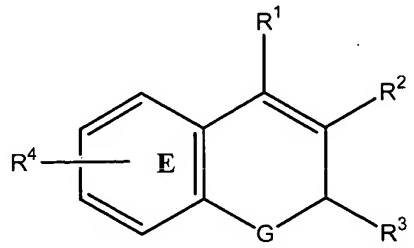
The invention is also directed to a novel composition comprising duloxetine, venlafaxine or atomoxetine (or combinations thereof) and a COX-2 inhibitor, wherein the cyclooxygenase-2 selective inhibitor comprises 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, having the formula:



or a prodrug thereof.

The invention is also directed to a novel composition comprising duloxetine, venlafaxine or atomoxetine (or combinations thereof) and a COX-2 inhibitor, wherein the cyclooxygenase-2 selective inhibitor comprises a chromene that is a substituted benzopyran, or is a chroman.

The invention is also directed to a novel composition comprising duloxetine, venlafaxine or atomoxetine (or combinations thereof) and a COX-2 inhibitor, wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of substituted benzothiopyrans,



dihydroquinolines, or dihydronaphthalenes having the general formula:

wherein G is selected from the group consisting of O or S or NR^a;

wherein R^a is alkyl;

wherein R^1 is selected from the group consisting of H and aryl;

wherein R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

wherein R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

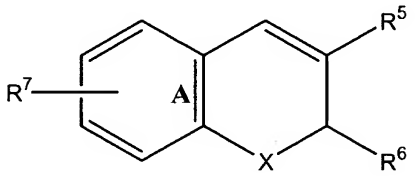
wherein R^4 is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R^4 together with ring ^{7}E forms a naphthyl radical;

or an isomer thereof; and

including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

The invention is also directed to a novel composition comprising duloxetine, venlafaxine or atomoxetine (or combinations thereof) and a COX-2 inhibitor, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the formula:



wherein:

X is selected from the group consisting of O or S or NR^b;

R^b is alkyl;

R^5 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

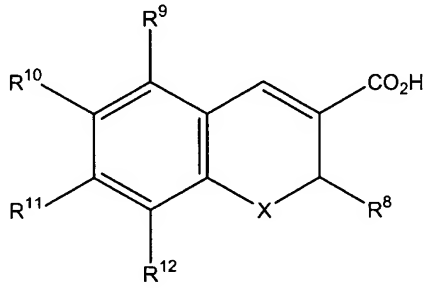
R^6 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

R^7 is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally

substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^7 together with ring A forms a naphthyl radical;

or a prodrug thereof.

The invention is also directed to a novel composition comprising duloxetine, venlafaxine or atomoxetine (or combinations thereof) and a COX-2 inhibitor, wherein the cyclooxygenase-2 specific inhibitor comprises a compound having the formula:



wherein:

X is selected from the group consisting of O and S;

R^8 is lower haloalkyl;

R^9 is selected from the group consisting of hydrido, and halo;

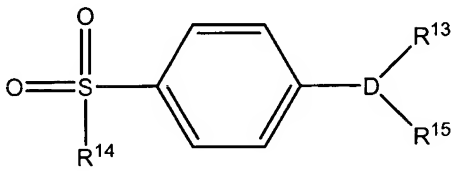
R^{10} is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6- membered nitrogen-containing heterocyclosulfonyl;

R^{11} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R^{12} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;

or an isomer or prodrug thereof.

The invention is also directed to a novel composition comprising duloxetine, venlafaxine or atomoxetine (or combinations thereof) and a COX-2 inhibitor, wherein the cyclooxygenase-2 selective inhibitor comprises a material selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure:



wherein:

D is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R^{13} is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^{13} is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

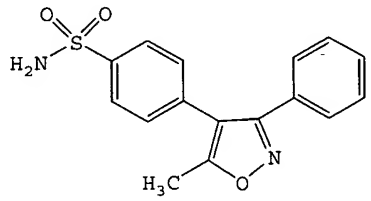
R^{14} is selected from the group consisting of methyl or amino; and

R^{15} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl,

aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

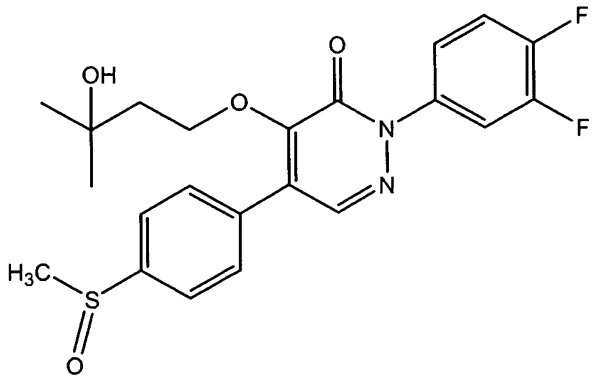
or a prodrug thereof.

The present invention is also directed to a novel composition comprising duloxetine, venlafaxine or atomoxetine (or combinations thereof) and a COX-2 inhibitor, wherein the cyclooxygenase-2 selective inhibitor comprises valdecoxib, having the following structure:



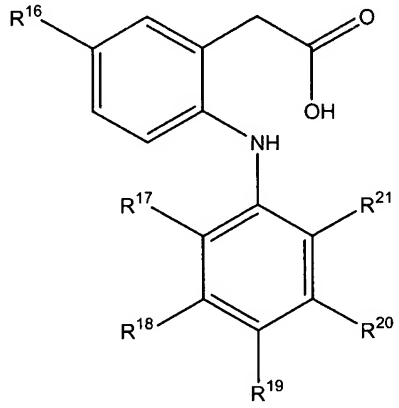
or a prodrug thereof.

The invention is also directed to a novel composition comprising duloxetine, venlafaxine or atomoxetine (or combinations thereof) and a COX-2 inhibitor, wherein the cyclooxygenase-2 selective inhibitor comprises a compound having the structure:



or a prodrug thereof.

The present invention is also directed to a novel composition comprising duloxetine, venlafaxine or atomoxetine (or combinations thereof) and a COX-2 inhibitor, wherein the cyclooxygenase-2 selective inhibitor comprises a phenylacetic acid derivative represented by the general structure:



wherein R^{16} is methyl or ethyl;

R^{17} is chloro or fluoro;

R^{18} is hydrogen or fluoro;

R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{20} is hydrogen or fluoro; and

R^{21} is chloro, fluoro, trifluoromethyl or methyl,

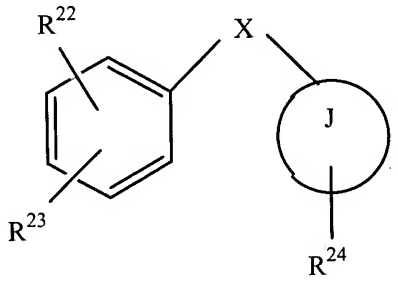
provided that R^{17}, R^{18}, R^{19} and R^{20} are not all fluoro when R^{16} is ethyl and R^{19} is H;

or a prodrug thereof.

The present invention is also directed to a novel composition comprising duloxetine, venlafaxine or atomoxetine (or combinations thereof) and a COX-2 inhibitor, wherein the cyclooxygenase-2 selective

inhibitor comprises BMS-347070 (See U.S. Pat. No. 6,180,651, incorporated herein by reference in its entirety).

The present invention is also directed to a novel composition comprising duloxetine, venlafaxine and/or atomoxetine and a COX-2 inhibitor, wherein the cyclooxygenase-2 selective inhibitor comprises a compound represented by the general structure:



or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

X is O or S;

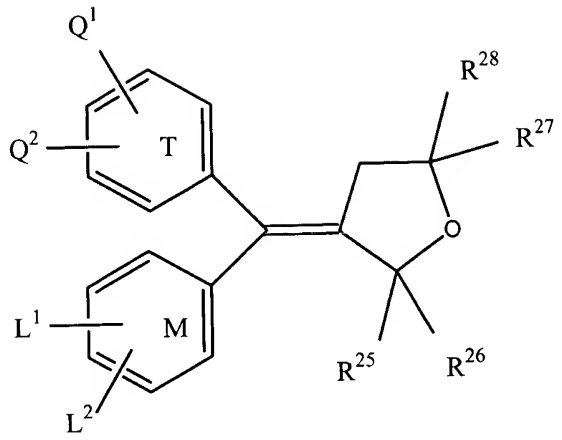
J is a carbocycle or a heterocycle;

R^{22} is $NHSO_2CH_3$ or F;

R^{23} is H, NO_2, or F; and

R^{24} is H, $NHSO_2CH_3$, or $(SO_2CH_3)C_6H_4$.

According to another embodiment, the invention is directed to a novel composition comprising duloxetine, venlafaxine and/or atomoxetine and a COX-2 inhibitor, wherein the cyclooxygenase-2 selective inhibitor comprises a compound represented by the general structure:



or an isomer or pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

T and M independently are phenyl, naphthyl, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

Q^1, Q^2, L^1 or L^2 are independently hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms, trifluoromethyl, or lower methoxy having from 1 to 6 carbon atoms; and

at least one of Q^1, Q^2, L^1 or L^2 is in the para position and is $-S(O)_n-R$, wherein n is 0, 1, or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms or a lower haloalkyl radical having from 1 to 6 carbon atoms, or an $-SO_2NH_2$; or,

Q^1 and Q^2 are methylenedioxy; or

L^1 and L^2 are methylenedioxy; and

R^{25}, R^{26}, R^{27}, and R^{28} are independently hydrogen, halogen, lower alkyl radical having from 1 to 6 carbon atoms, lower haloalkyl radical

having from 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R^{25} and R^{26} are O; or,

R^{27} and R^{28} are O; or,

R^{25}, R^{26}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms; or,

R^{27}, R^{28}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms.

The present invention is also directed to a pharmaceutical composition comprising duloxetine, venlafaxine or atomoxetine (or combinations thereof); a cyclooxygenase-2 specific inhibitor or prodrug thereof; and a pharmaceutically-acceptable excipient.

The present invention is also directed to a novel method of treating or preventing a cyclooxygenase-2 mediated disorder in a subject, said method comprising treating the subject having or susceptible to said disorder with a therapeutically-effective amount of the pharmaceutical compositions that comprise duloxetine, venlafaxine or atomoxetine (or combinations thereof) and any one of the cyclooxygenase-2-selective inhibitors described above.

Several advantages are achieved by the present invention, including the provision of an improved method and a composition that prevent, inhibit, or treat a CNS disorder and/or pain (*e.g.*, neuropathic pain) and inflammation or an inflammation-associated disorder, and also a method and a composition that are efficacious for such applications in physiologically acceptable dosages, and that are selective in their physiological impact.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention, it has been discovered that a CNS disorder and/or pain (*e.g.*, neuropathic pain) and inflammation or an inflammation-associated disorder can be treated, prevented, or

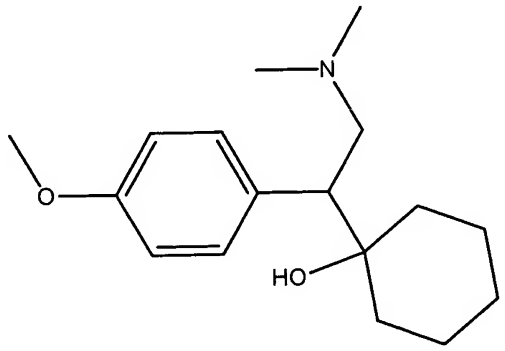
inhibited in a subject that is in need of such treatment, prevention, or inhibition by administering to the subject a combination of therapeutic agents that includes duloxetine, venlafaxine or atomoxetine (or any combination thereof: duloxetine/venlafaxine; duloxetine/atomoxetine, venlafaxine/atomoxetine; or duloxetine/venlafaxine/atomoxetine) and a cyclooxygenase-2 selective inhibitor. The amount of the duloxetine, venlafaxine or atomoxetine (or any combination thereof: duloxetine/venlafaxine; duloxetine/atomoxetine, venlafaxine/atomoxetine; or duloxetine/venlafaxine/atomoxetine) and the amount of the cyclooxygenase-2-selective inhibitor that are used in combination in the treatment can be selected so that together they constitute an effective amount for the treatment, prevention, or inhibition of a CNS disorder and/or pain and inflammation or an inflammation-associated disorder.

The novel method of treating a subject with a combination of duloxetine, venlafaxine or atomoxetine (or any combination thereof: duloxetine/venlafaxine; duloxetine/atomoxetine, venlafaxine/atomoxetine; or duloxetine/venlafaxine/atomoxetine) and a cyclooxygenase-2-selective inhibitor provides a safe and efficacious method for preventing and alleviating pain and inflammation and for preventing and treating disorders that are associated with inflammation. In addition to being an efficacious method and composition for preventing and/or alleviating pain and inflammation in a treated subject, such method and composition might also provide desirable properties such as stability, ease of handling, ease of compounding, lack of side effects, ease of preparation or administration, and the like.

The novel method and compositions comprise the use of duloxetine, venlafaxine or atomoxetine (or any combination thereof: duloxetine/venlafaxine; duloxetine/atomoxetine, venlafaxine/atomoxetine; or duloxetine/venlafaxine/atomoxetine or any other NRI substituted for any

of duloxetine, venlafaxine or atomoxetine) and a cyclooxygenase-2 selective inhibitor.

Venlafaxine that is useful in the present invention may be obtained from any source of the same. Venlafaxine is 1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol and its preparation is described in U.S.

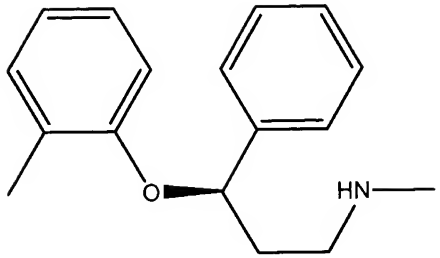


1-[(2-dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol = venlafaxine

Pat. Nos. 4,535,186 and 4,761,501. The structure of venlafaxine is:

Venlafaxine is both a SSRI (serotonin specific reuptake inhibitor) and a NRI (norepinephrine reuptake inhibitor). Velaxafine is described in one or more of the following U.S. patents: 6,290,986 B1; 6,229,010 B1; 6,096,742 B1; 6,191,133 B1; 6,184,222 B1; 6,066,643; 6,028,070; 4,761,501; 4,535,186 and 6,274,171 B2.

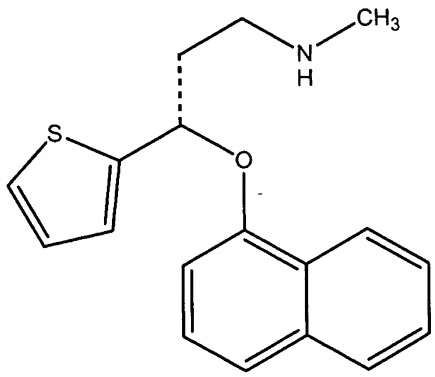
Atomoxetine that is useful in the present invention may be obtained from any source of the same. Atomexetine is a SSRI and a NRI. Atomoxetine is (R)-(-)-N-methyl-3-(2-methylphenoxy)-3-phenylpropylamine = (R) -tomoxetine and its preparation is described in U.S. Pat. No. 4,314,081. The structure of atomoxetine is:



(R)-(-)-N-methyl-3-(2-methylphenoxy)-3-phenylpropylamine = (R) -tomoxetine = atomoxetine

Atomoxetine is described in one or more of the following U.S. patents: 6,184,222 B1; 6,066,043; and 6,028,070.

Duloxetine is both a SSRI and a NRI. Duloxetine is Methyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-amine and its preparation is described in U.S. Pat. No. 5,023,269. The structure of duloxetine is:



Methyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-amine

(duloxetine)

See also U.S. Pat. No. 5,362,886 for an improved process for preparing duloxetine.

As used herein, the term "purified" means partially purified and/or completely purified. Thus a "purified composition" may be either partially

purified or completely purified. Typically, duloxetine, venlafaxine or atomoxetine is synthesized according to methods well known to those skilled in the art. Venlafaxine is often provided as a racemic mixture, but may be used in enantiomerically pure form or a form having an enantiomeric excess of one racemate over another. The duloxetine, venlafaxine or atomoxetine that is useful in the subject composition and associated method can be of any purity and quality that is pharmaceutically acceptable.

In an embodiment of the present invention, duloxetine, venlafaxine or atomoxetine (or combinations thereof) is combined with a cyclooxygenase-2 selective inhibitor. Any cyclooxygenase-2 selective inhibitor or prodrug thereof that meets the criteria described below can be used in the subject method.

As used herein, the term "cyclooxygenase-2 inhibitor", embraces compounds that selectively inhibit cyclooxygenase-2 over cyclooxygenase-1, and also includes pharmaceutically acceptable salts of those compounds.

In practice, the selectivity of a COX-2 inhibitor varies depending upon the condition under which the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of a COX-2 inhibitor can be measured as a ratio of the *in vitro* or *in vivo* IC_{50} value for inhibition of COX-1, divided by the IC_{50} value for inhibition of COX-2 (COX-1 IC_{50}/COX-2 IC_{50}). A COX-2 selective inhibitor is any inhibitor for which the ratio of COX-1 IC_{50} to COX-2 IC_{50} (*i.e.*, the selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition) is greater than 1, preferably greater than 1.5, more preferably greater than 2, even more preferably greater than 5, still more preferably greater than 10, yet more preferably greater than 50, and more preferably still greater than 100.

As used herein, the term "IC_{50}" refers to the concentration of a compound that is required to produce 50% inhibition of cyclooxygenase activity.

Preferably, cyclooxygenase-2 selective inhibitors of the present invention have a cyclooxygenase-2 IC_{50} of less than about 5 μM, more preferably less than about 1 μM, and even more preferably less than about 0.2 μM.

Preferably, cycloxoygenase-2 selective inhibitors have a cyclooxygenase-1 IC_{50} of greater than about 1 μM, more preferably greater than about 10 μM, and even more preferably greater than about 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

Also included within the scope of the present invention are compounds that act as prodrugs of cyclooxygenase-2-selective inhibitors. As used herein in reference to COX-2 selective inhibitors, the term "prodrug" refers to a chemical compound that is converted into an active COX-2 selective inhibitor by metabolic processes within the body. One example of a prodrug for a COX-2 selective inhibitor is parecoxib, which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-2 selective inhibitor valdecoxib. An example of a preferred COX-2 selective inhibitor prodrug is sodium parecoxib.

The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH_2-) radical. Where used, either alone or within other terms such as "haloalkyl", "alkylsulfonyl", "alkoxyalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl"

radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about six carbon atoms.

Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.

The term "alkenyl" embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl.

The term "alkynyl" denotes linear or branched radicals having two to about twenty carbon atoms or, preferably, two to about twelve carbon atoms. More preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms. Most preferred are lower alkynyl radicals having two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

The terms "alkenyl", "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "cycloalkyl" embraces saturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to about eight carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "cycloalkenyl" embraces partially unsaturated carbocyclic radicals having three to twelve carbon atoms. More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl, cyclopentadienyl and cyclohexenyl.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above.

Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having one to six carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

The terms "alkoxy" and "alkyloxy" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. The term "alkoxyalkyl" embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy radicals. More preferred haloalkoxy radicals are "lower haloalkoxy" radicals having one to six carbon atoms and one or more halo radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. Aryl moieties may also be substituted at a substitutable position with one or more substituents selected independently from alkyl, alkoxyalkyl, alkylaminoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkoxy, aralkoxy, hydroxyl, amino, halo, nitro, alkylamino, acyl, cyano, carboxy, aminocarbonyl, alkoxycarbonyl and aralkoxycarbonyl.

The terms "heterocyclo", "heterocyclyl", and "heterocycle" embrace saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Examples of saturated heterocyclo, heterocyclyl, and heterocycle radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms (*e.g.*, pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (*e.g.*, morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (*e.g.*, thiazolidinyl, etc.). Examples of partially unsaturated heterocyclo, heterocyclyl, and heterocycle radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

The term "heteroaryl" embraces unsaturated heterocyclo radicals. Examples of unsaturated heterocyclo radicals, also termed "heteroaryl" radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (*e.g.*, 4H-1,2,4-triazolyl, lH-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (*e.g.*, lH-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed

heterocyclo group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (*e.g.*, tetrazolo[l,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (*e.g.*, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclo group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (*e.g.*, benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic: group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (*e.g.*, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclo group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (*e.g.*, benzothiazolyl, benzothiadiazolyl, etc.) and the like. The term also embraces radicals where heterocyclo radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, benzopyran, and the like. Said "heterocyclo group" may have 1 to 3 substituents such as alkyl, hydroxyl, halo, alkoxy, oxo, amino and alkylamino.

The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to about ten carbon atoms attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthio radicals are methylthio, ethylthio, propylthio, butylthio and hexylthio. The term "alkylthioalkyl" embraces radicals containing an alkylthio radical attached through the divalent sulfur atom to an alkyl radical of one to about ten carbon atoms. More preferred alkylthioalkyl

radicals are "lower alkylthioalkyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylthioalkyl radicals include methylthiomethyl.

The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent -S(=O)- radical. More preferred alkylsulfinyl radicals are "lower alkylsulfinyl" radicals having alkyl radicals of one to six carbon atoms. Examples of such lower alkylsulfinyl radicals include methylsulfinyl, ethylsulfinyl, butylsulfinyl and hexylsulfinyl.

The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are "lower alkylsulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The "alkylsulfonyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide haloalkylsulfonyl radicals.

The terms "sulfamyl", "aminosulfonyl" and "sulfonamidyl" denote NH_2O_2S-.

The term "acyl" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. Examples of such acyl radicals include alkanoyl and aroyl radicals. Examples of such lower alkanoyl radicals include formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl and trifluoroacetyl.

The term "carbonyl", whether used alone or with other terms, such as "alkoxycarbonyl", denotes -(C=O)-. The term "aroyl" embraces aryl radicals with a carbonyl radical as defined above. Examples of aroyl include benzoyl, naphthoyl, and the like and the aryl in said aroyl may be additionally substituted.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2H$. The term "carboxyalkyl" embraces alkyl radicals substituted with a carboxy radical. More preferred are "lower carboxyalkyl" which embrace lower alkyl radicals as defined above, and may be additionally substituted on the alkyl radical with halo. Examples of such lower carboxyalkyl radicals include carboxymethyl, carboxyethyl and carboxypropyl. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. More preferred are "lower alkoxycarbonyl" radicals with alkyl portions having 1 to 6 carbons. Examples of such lower alkoxycarbonyl (ester) radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl.

The terms "alkylcarbonyl", "arylcarbonyl" and "aralkylcarbonyl" include radicals having alkyl, aryl and aralkyl radicals, as defined above, attached to a carbonyl radical. Examples of such radicals include substituted or unsubstituted methylcarbonyl, ethylcarbonyl, phenylcarbonyl and benzylcarbonyl.

The term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The terms benzyl and phenylmethyl are interchangeable.

The term "heterocycloalkyl" embraces saturated and partially unsaturated heterocyclo-substituted alkyl radicals, such as pyrrolidinylmethyl, and heteroarylsubstituted alkyl radicals, such as pyridylmethyl, quinolylmethyl, thienylmethyl, furylethyl, and quinolylethyl. The heteroaryl in said heteroaralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy.

The term "aralkoxy" embraces aralkyl radicals attached through an oxygen atom to other radicals. The term "aralkoxyalkyl" embraces aralkoxy radicals attached through an oxygen atom to an alkyl radical. The term "aralkylthio" embraces aralkyl radicals attached to a sulfur atom. The term "aralkylthioalkyl" embraces aralkylthio radicals attached through a sulfur atom to an alkyl radical.

The term "aminoalkyl" embraces alkyl radicals substituted with one or more amino radicals. More preferred are "lower aminoalkyl" radicals. Examples of such radicals include aminomethyl, aminoethyl, and the like. The term "alkylamino" denotes amino groups that have been substituted with one or two alkyl radicals. Preferred are "lower N-alkylamino" radicals having alkyl portions having 1 to 6 carbon atoms. Suitable lower alkylamino may be mono or dialkylamino such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like. The term "arylamino" denotes amino groups that have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aralkylamino" embraces aralkyl radicals attached through an amino nitrogen atom to other radicals. The terms "N-arylaminoalkyl" and "N-aryl-N-alkylaminoalkyl" denote amino groups which have been substituted with one aryl radical or one aryl and one alkyl radical, respectively, and having the amino group attached to an alkyl radical. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl.

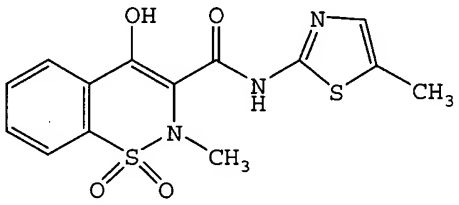
The term "aminocarbonyl" denotes an amide group of the formula -$C(=O)NH_2$. The term "alkylaminocarbonyl" denotes an aminocarbonyl group that has been substituted with one or two alkyl radicals on the amino nitrogen atom. Preferred are "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" radicals. More preferred are "lower N-alkylaminocarbonyl" and "lower N,N-dialkylaminocarbonyl" radicals with lower alkyl portions as defined above. The term "aminocarbonylalkyl"

denotes a carbonylalkyl group that has been substituted with an amino radical on the carbonyl carbon atom.

The term "alkylaminoalkyl" embraces radicals having one or more alkyl radicals attached to an aminoalkyl radical. The term "aryloxyalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent oxygen atom. The term "arylthioalkyl" embraces radicals having an aryl radical attached to an alkyl radical through a divalent sulfur atom.

As used herein, the term "carbocycle" means a hydrocarbon ring radical. Carbocyclic rings are monocyclic or are fused, bridged, or spiro polycyclic rings. Unless otherwise specified, monocyclic rings contain from 3 to about 9 atoms, preferably from about 4 to about 7 atoms, and most preferably 5 or 6 atoms. Polycyclic rings contain from about 7 to about 17 atoms, preferably from about 7 to about 14 atoms, and most preferably 9 or 10 atoms. Carbocyclic rings (carbocycles) may be substituted or unsubstituted.

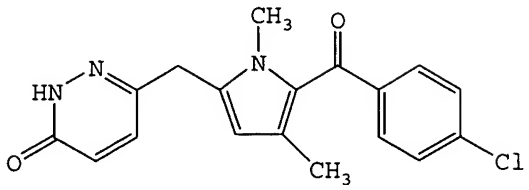
The cyclooxygenase-2 selective inhibitor of the present invention can be, for example, the COX-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7), or a pharmaceutically acceptable salt or prodrug thereof.



B-1

In another embodiment of the invention the cyclooxygenase-2 selective inhibitor can be the COX-2 selective inhibitor RS 57067, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically

acceptable salt or prodrug thereof.

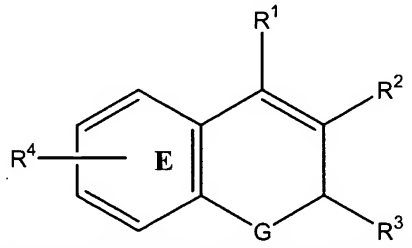


B-2

In a preferred embodiment of the invention the cyclooxygenase-2 selective inhibitor is of the chromene structural class that is a substituted benzopyran or a substituted benzopyran analog, and even more preferably selected from the group consisting of substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the structure of any one of the compounds having a structure shown by general Formulas I, II, or III, shown below, and possessing, by way of example and not limitation, the structures disclosed in Table 1, including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

Furthermore, benzopyran COX-2 selective inhibitors useful in the practice of the present invention are described in U.S. Patent No. 6,034,256 and 6,077,850.

Formula I is:



I

wherein G is selected from the group consisting of O or S or NR^a;

wherein R^a is alkyl;

wherein R^1 is selected from the group consisting of H and aryl;

wherein R^2 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

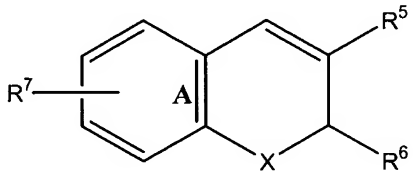
wherein R^3 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and

wherein R^4 is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;

or wherein R^4 together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof; and

including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

Formula II is:



II

wherein:

X is selected from the group consisting of O or S or NR^b;

R^b is alkyl;

R^5 is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^6 is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl

each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

R^7 is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^7 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula II, wherein:

X is selected from the group consisting of oxygen and sulfur;

R^5 is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^6 is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

R^7 is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered-nitrogen containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or

wherein R^7 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula II, wherein:

R^5 is carboxyl;

R^6 is lower haloalkyl; and

R^7 is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or wherein R^7 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula II, wherein:

R^6 is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

R^7 is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or wherein R^2 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

The cyclooxygenase-2 selective inhibitor may also be a compound of Formula II, wherein:

R^6 is selected from the group consisting trifluoromethyl and pentafluoroethyl; and

R^7 is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl; or wherein R^7 together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

Other compounds that are useful for the cyclooxygenase-2 selective inhibitor include:

6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-27);

6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-28);

8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-29);

6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-30);

2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid (B-31);

7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-32);

6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-33);

8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-34);

6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-35);

5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-36);

8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-37);

7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-38);

6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-39);

7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-40);

7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-41);

6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-42);

6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-43);

6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-44);

6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-45);

6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-46);

6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-47);

8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-48)

8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-49);

6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-50);

8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-51);

8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-52);

8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-53);

6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-54);

6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-55);

6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-56);

6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-57);

6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-58);

6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-59);

6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-60);

6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-61);

6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-62);

8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-63);

6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-64);

6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-65);

8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-66);

6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-67);

6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-68);

6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-69);

6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-70);

6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-71);

7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid (B-72);

6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-73);

3-[(3-Chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene]-dihydro-furan-2-one or BMS-347070 (B-74);

8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine (B-75);

5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone (B-76);

5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (B-77);

4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole (B-78);

4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-79);

4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-80);

4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide (B-81);

4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-82);

4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-83);

4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-84);

4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide (B-85);

4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide (B-86);

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-87);

4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-88);

4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-89);

4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-90);

4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-91);

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-92);

4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-93);

4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-94);

4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide (B-95);

4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-96);

4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-97);

4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-98);

4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-99);

4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide (B-100);

4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-101);
4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-102);
5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-103);
4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (B-104);
6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene (B-105);
5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-106);
4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (B-107);
5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-108);
5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene (B-109);
4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide (B-110);
2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (B-111);
2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole (B-112);
5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole (B-113);
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-114);
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole (B-115);
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole (B-116);
4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole (B-117);

2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole (B-118);

5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole (B-119);

1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene (B-120);

4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide (B-121);

5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene (B-122);

4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide (B-123);

6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-124);

2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile (B-125);

6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile (B-126);

4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-127);

4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-128);

4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-129);

3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-130);

2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-131);

2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-132);

2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine (B-133);

4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-134);

2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (B-135);

4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-136);

2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole (B-137);

2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole (B-138);

2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole (B-139);

2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole (B-140);

1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole (B-141);

2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-142);

4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-143);

2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole (B-144);

4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-145);

2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole (B-146);

4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-147);

1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole (B-148);

4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-149);

4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-150);

4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide (B-151);

1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole (B-152);

4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide (B-153);

N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide (B-154);

ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate (B-155);

4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole (B-156);

4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole (B-157);

1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole (B-158);

5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole (B-159);

4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole (B-160);

5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-161);

2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-162);

5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine (B-163);

2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine (B-164);

4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide (B-165);

1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene (B-166);

5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole (B-167);

4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide (B-168);

4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-169);

4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-170);

4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide (B-171);

1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-172);

1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-173);

1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-174);

1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-175);

1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-176);

1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-177);

1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-178);

4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide (B-179);

1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-180);

4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide (B-181);

4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-182);
4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-183);
1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-184);
1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-185);
4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide (B-186);
1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene (B-187);
4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide (B-188);
4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide (B-189);
ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate (B-190);
2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid (B-191);
2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole (B-192);
4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole (B-193);
4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole (B-194);
4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide (B-195);
6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-196);
6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid (B-197);
5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone (B-198);
6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid (B-199);

4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-200);
4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-201);
4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (B-202);
3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-203);
2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine (B-204);
4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide (B-205);
4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-206);
4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide (B-207);
[2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide (B-208);
4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide (B-209);
4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide (B-210);
[2-(2,4-dichloro-6-methyl-phenylamino)-5-ethyl-phenyl]-acetic acid or COX 189 (B-211);
N-(4-Nitro-2-phenoxy-phenyl)-methanesulfonamide or nimesulide (B-212);
N-[6-(2,4-difluoro-phenoxy)-1-oxo-indan-5-yl]-methanesulfonamide or flosulide (B-213);
N-[6-(2,4-Difluoro-phenylsulfanyl)-1-oxo-1H-inden-5-yl]-methanesulfonamide, soldium salt or L-745337 (B-214);
N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide or RWJ-63556 (B-215);
3-(3,4-Difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl-5-(2,2,2-trifluoro-ethyl)-5H-furan-2-one or L-784512 or L-784512 (B-216);

(5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4(5H)-thiazolone or darbufelone (B-217);

CS-502 (B-218);

LAS-34475 (B-219);

LAS-34555 (B-220);

S-33516 (B-221);

SD-8381 (B-222);

L-783003 (B-223);

N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide or T-614 (B-224);

D-1367 (B-225);

L-748731 (B-226);

(6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid or CT3 (B-227);

CGP-28238 (B-228);

4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one or BF-389 (B-229);

GR-253035 (B-230);

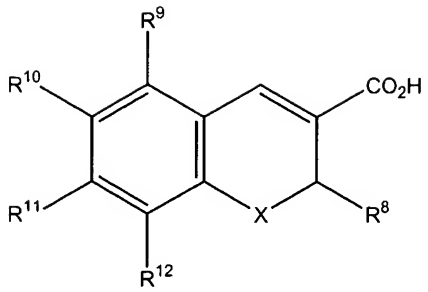
6-dioxo-9H-purin-8-yl-cinnamic acid (B-231);

S-2474 (B-232); or

meloxicam (B-233)

or an isomer, a pharmaceutically acceptable salt, ester or prodrug thereof, respectively.

The cyclooxygenase-2 selective inhibitor of the present invention can also be a compound having the structure of Formula III:



III

wherein:

X is selected from the group consisting of O and S;

R^8 is lower haloalkyl;

R^9 is selected from the group consisting of hydrido, and halo;

R^{10} is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6- membered nitrogen-containing heterocyclosulfonyl;

R^{11} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R^{12} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;

or an isomer or prodrug thereof.

The cyclooxygenase-2 selective inhibitor can also be a compound of having the structure of Formula III, wherein

R^8 is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

R^9 is selected from the group consisting of hydrido, chloro, and fluoro;

R^{10} is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl,

benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

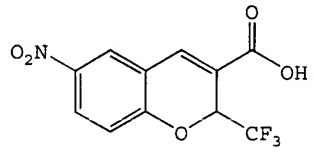
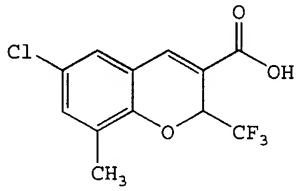
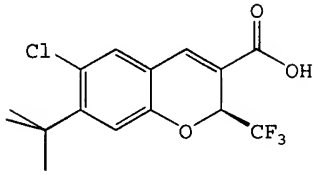
R^{11} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

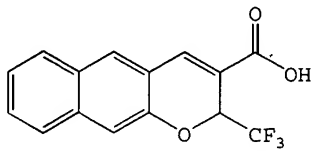
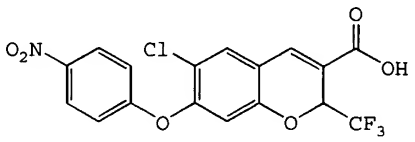
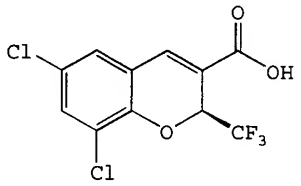
R^{12} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;

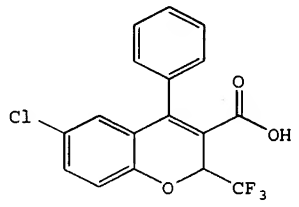
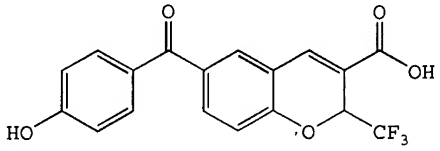
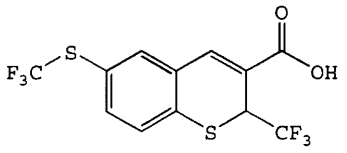
or an isomer or prodrug thereof.

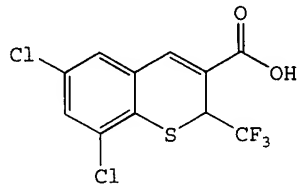
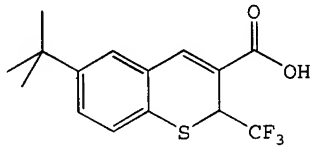
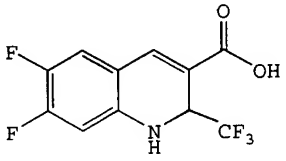
The present invention is also directed to a novel composition wherein the cyclooxygenase-2 selective inhibitor comprises BMS-347070.

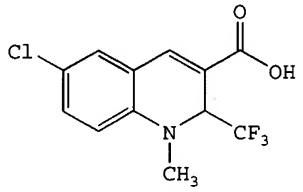
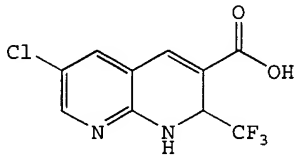
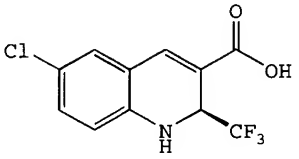
Table 1. Examples of Chromene COX-2 Selective Inhibitors as Embodiments

Compound Number	Structural Formula
B-3	 6-Nitro-2-trifluoromethyl-2H-1 -benzopyran-3-carboxylic acid
B-4	 6-Chloro-8-methyl-2-trifluoromethyl -2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluo romethyl-2H-1-benzopyran-3-carboxylic acid

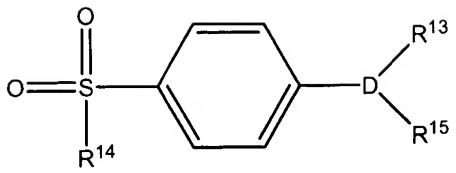
Compound Number	Structural Formula
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b] pyran-3-carboxylic acid
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran=3=carboxylic acid
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid

Compound Number	Structural Formula
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

Compound Number	Structural Formula
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoro methyl)-3-quinolinecarboxylic acid
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro [1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoro methyl)-3-quinolinecarboxylic acid

In a further preferred embodiment of the invention the cyclooxygenase inhibitor can be selected from the class of tricyclic cyclooxygenase-2 selective inhibitors represented by the general structure of Formula IV:



IV

wherein:

D is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R^{13} is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^{13} is optionally substituted at a substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^{14} is selected from the group consisting of methyl or amino; and

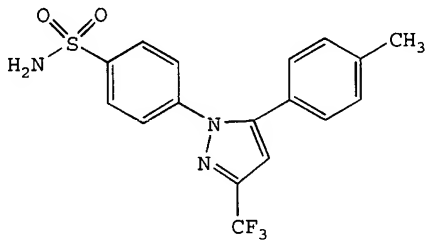
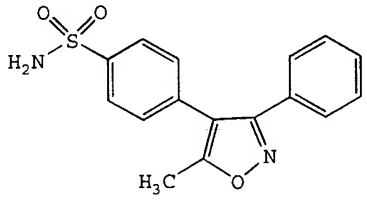
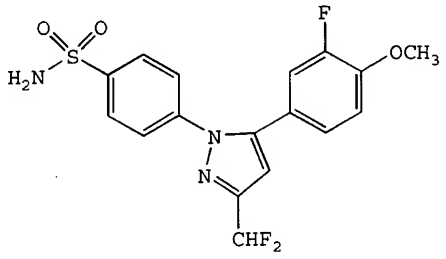
R^{15} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl,

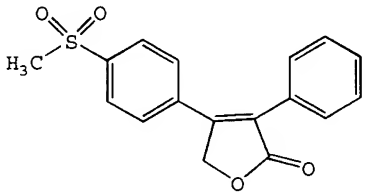
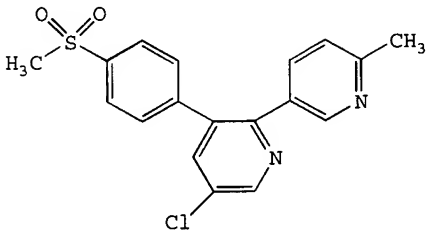
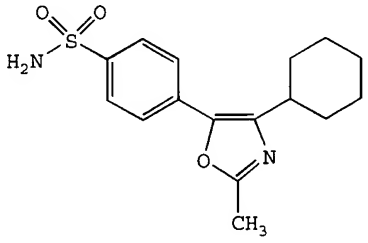
alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

or a prodrug thereof.

In a still more preferred embodiment of the invention, the cyclooxygenase-2 selective inhibitor represented by the above Formula IV is selected from the group of compounds, illustrated in Table 2, consisting of celecoxib (B-18), valdecoxib (B-19), deracoxib (B-20), rofecoxib (B-21), etoricoxib (MK-663; B-22), JTE-522 (B-23), or a prodrug thereof.

Table 2. Examples of Tricyclic COX-2 Selective Inhibitors as Embodiments

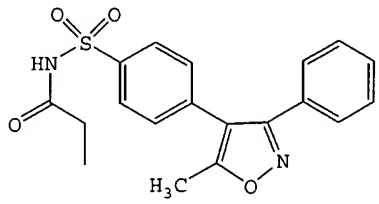
Compound Number	Structural Formula
B-18	
B-19	
B-20	

Compound Number	Structural Formula
B-21	
B-22	
B-23	

In an even more preferred embodiment of the invention, the COX-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

In another preferred embodiment of the invention, parecoxib, B-24, which is a therapeutically effective prodrug of the tricyclic cyclooxygenase-

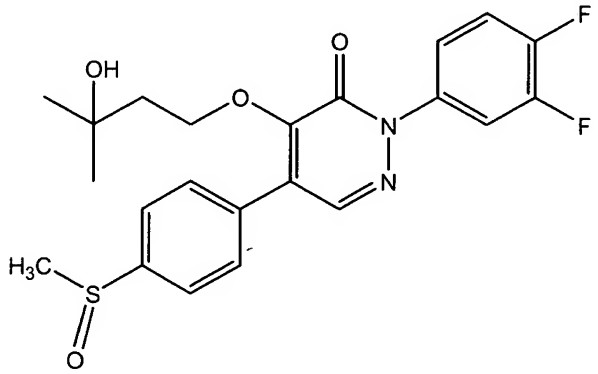
2 selective inhibitor valdecoxib, B-19, may be advantageously employed as a source of a cyclooxygenase inhibitor (See, *e.g.,* US 5,932,598).



B-24

A preferred form of parecoxib is sodium parecoxib.

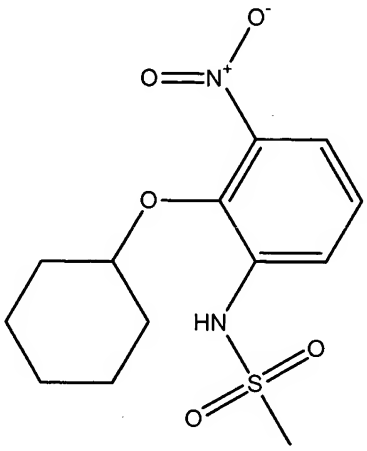
In another preferred embodiment of the invention, the compound ABT-963 having the formula B-25 that has been previously described in International Publication number WO 00/24719, is another tricyclic cyclooxygenase-2 selective inhibitor which may be advantageously employed.



B-25

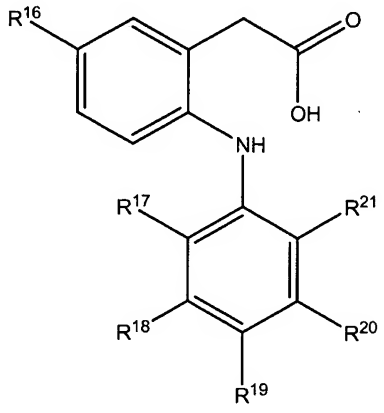
Another preferred cyclooxygenase-2 selective inhibitor that is useful in the present invention is N-(2-cyclohexyloxynitrophenyl)methane sulfonamide (NS-398) -- having a structure shown below as B-26. Applications of this compound have been described by, for example, Yoshimi, N. *et al.,* in *Japanese J. Cancer Res., 90(4):*406 - 412 (1999);

Falgueyret, J.-P. *et al.,* in *Science Spectra,* available at: http://www.gbhap.com/Science_Spectra/20-1-article.htm (06/06/2001); and Iwata, K. *et al.,* in *Jpn. J. Pharmacol., 75(2):*191 - 194 (1997).



B-26

In a further preferred embodiment of the invention the cyclooxygenase inhibitor can be selected from the class of phenylacetic acid derivative cyclooxygenase-2 selective inhibitors represented by the general structure of Formula V:



V

wherein R^{16} is methyl or ethyl;

R^{17} is chloro or fluoro;

R^{18} is hydrogen or fluoro;

R^{19} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;

R^{20} is hydrogen or fluoro; and

R^{21} is chloro, fluoro, trifluoromethyl or methyl,

provided that R^{17}, R^{18}, R^{19} and R^{20} are not all fluoro when R^{16} is ethyl and R^{19} is H.

A particularly preferred phenylacetic acid derivative cyclooxygenase-2 selective inhibitor is a compound that has the designation of COX189 and that has the structure shown in Formula V,

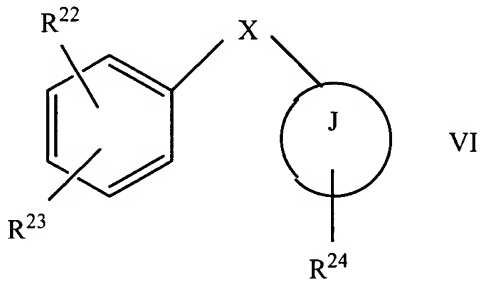
wherein R^{16} is ethyl;

R^{17} and R^{19} are chloro;

R^{18} and R^{20} are hydrogen; and

and R^{21} is methyl.

In a further preferred embodiment of the invention the cyclooxygenase inhibitor can be selected from the class of cyclooxygenase-2 selective inhibitors represented by the general structure of Formula VI:



VI

or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

X is O or S;

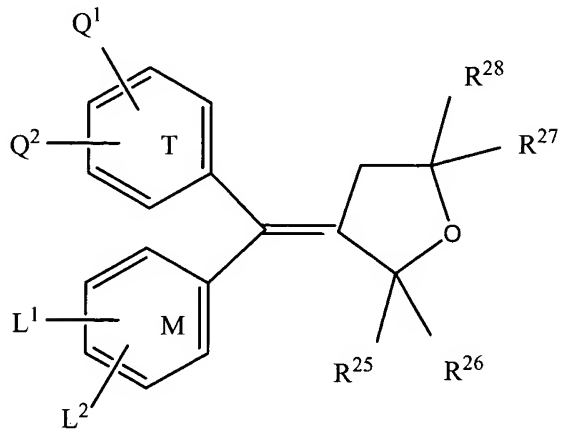
J is a carbocycle or a heterocycle;

R^{22} is $NHSO_2CH_3$ or F;

R^{23} is H, NO_2, or F; and

R^{24} is H, $NHSO_2CH_3$, or $(SO_2CH_3)C_6H_4$.

In a further preferred embodiment of the invention the cyclooxygenase inhibitor can be selected from the class of cyclooxygenase-2 selective inhibitors represented by the general structure of Formula VII:



VII

or an isomer or pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

T and M independently are phenyl, naphthyl, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

Q^1, Q^2, L^1 or L^2 are independently hydrogen, halogen, lower alkyl having from 1 to 6 carbon atoms, trifluoromethyl, or lower methoxy having from 1 to 6 carbon atoms; and

at least one of Q^1, Q^2, L^1 or L^2 is in the para position and is $-S(O)_n-R$, wherein n is 0, 1, or 2 and R is a lower alkyl radical having 1 to 6

carbon atoms or a lower haloalkyl radical having from 1 to 6 carbon atoms, or an $-SO_2NH_2$; or,

Q^1 and Q^2 are methylenedioxy; or

L^1 and L^2 are methylenedioxy; and

R^{25}, R^{26}, R^{27}, and R^{28} are independently hydrogen, halogen, lower alkyl radical having from 1 to 6 carbon atoms, lower haloalkyl radical having from 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

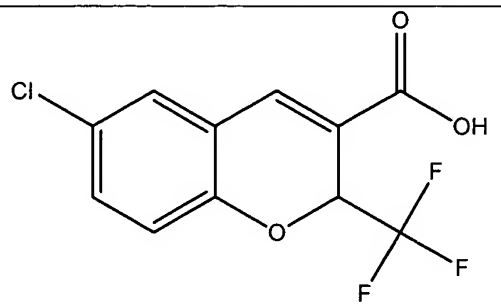
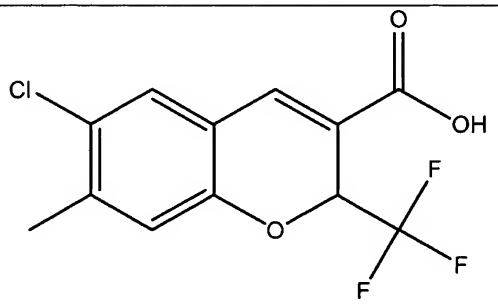
R^{25} and R^{26} are O; or,

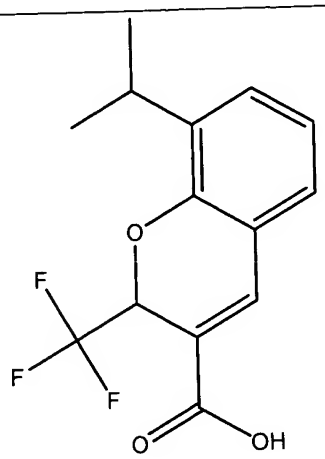
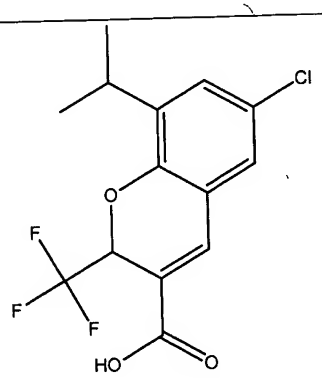
R^{27} and R^{28} are O; or,

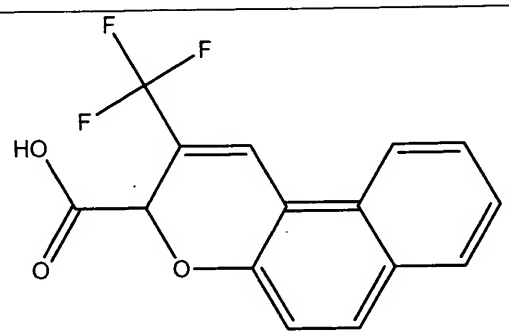
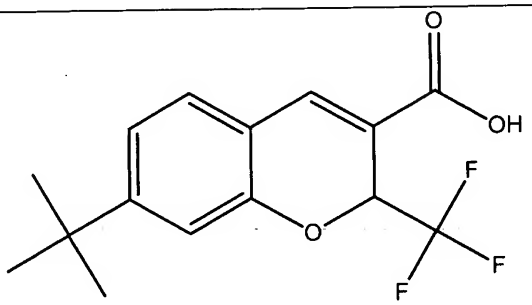
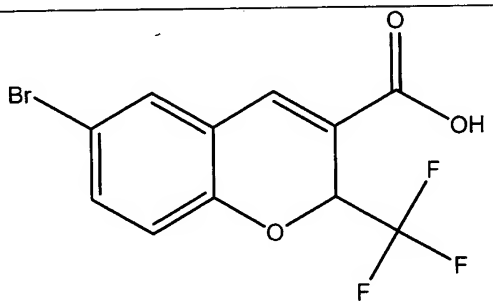
R^{25}, R^{26}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms; or,

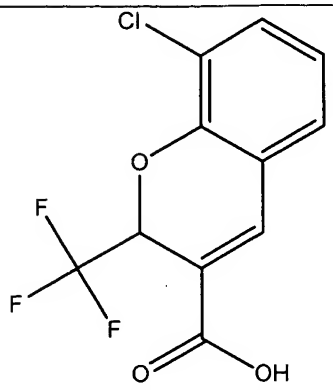
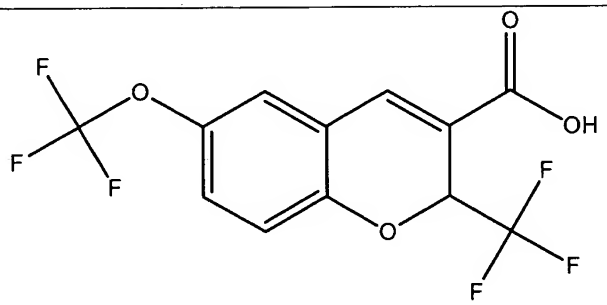
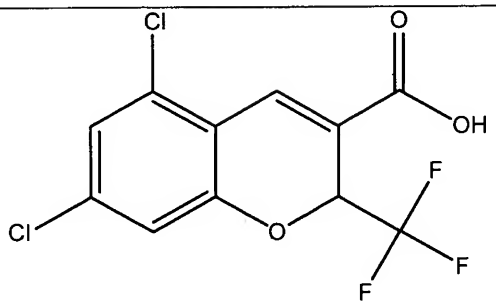
R^{27}, R^{28}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms.

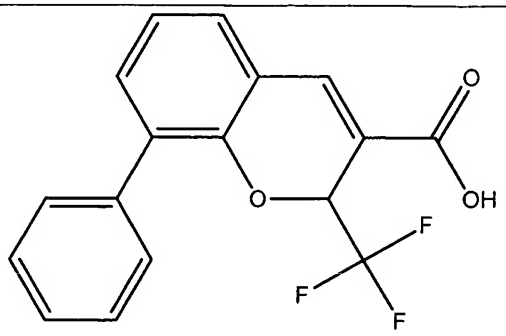
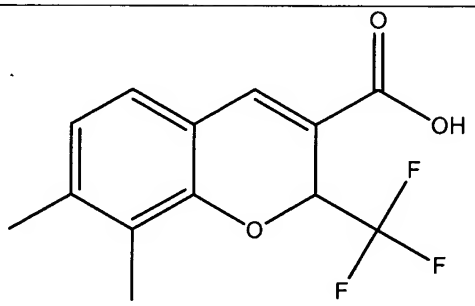
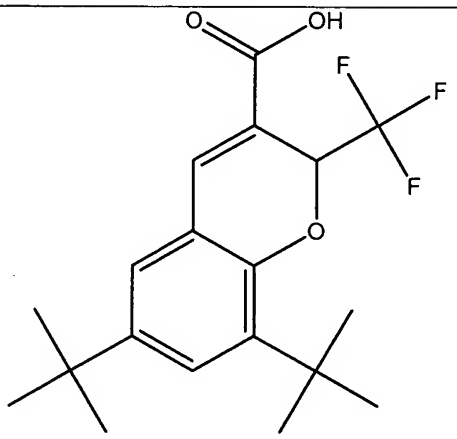
Other cyclooxygenase-2 selective inhibitors include, but are not limited to, the compounds B-27 to B-233 given below:

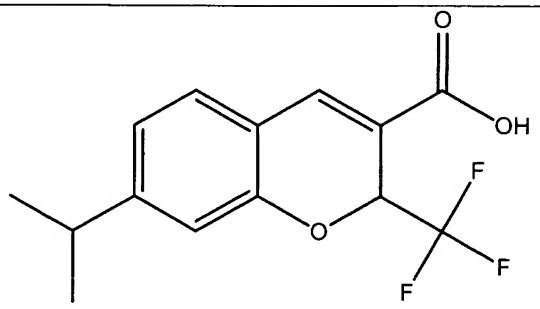
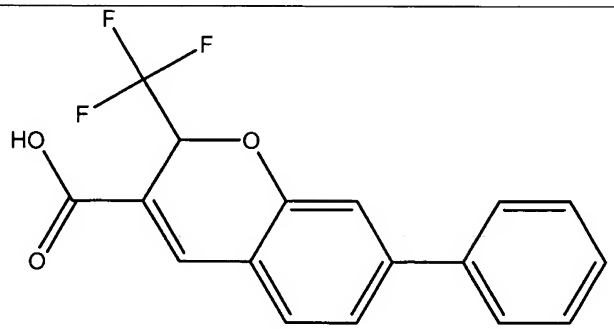
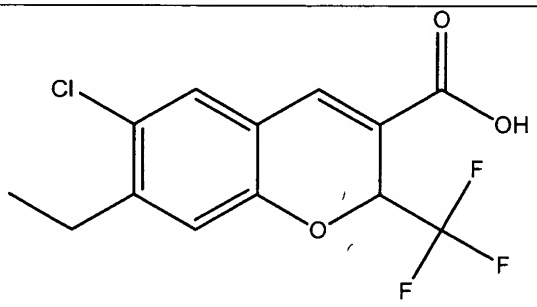
Compound	Name and/or Structure (COX 2 Inhibitor)
B-27	 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-28	 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

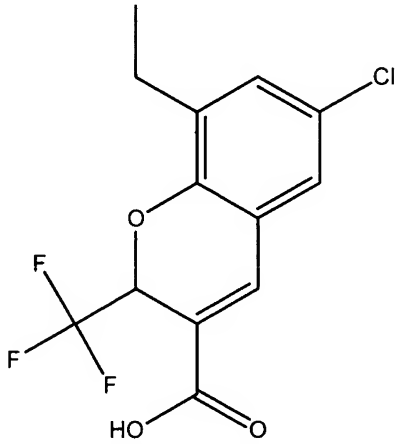
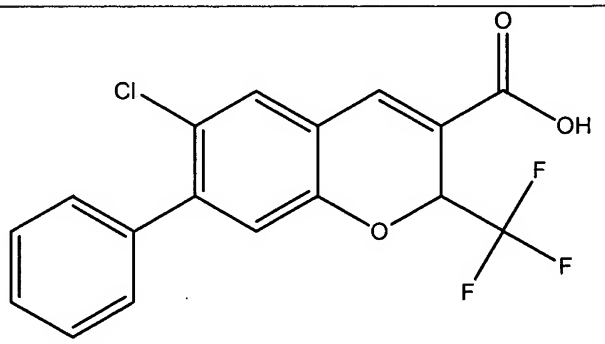
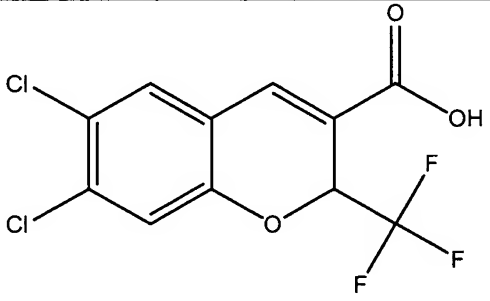
Compound	Name and/or Structure (COX 2 Inhibitor)
B-29	 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-30	 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

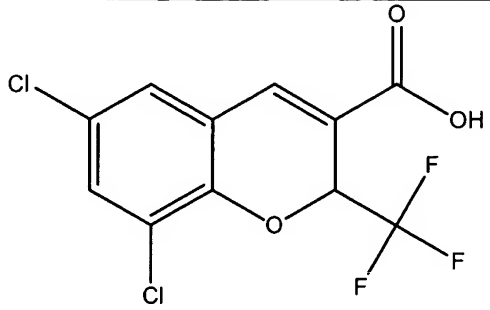
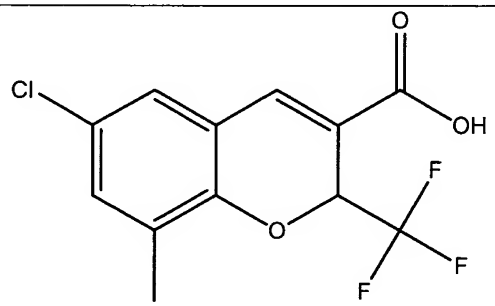
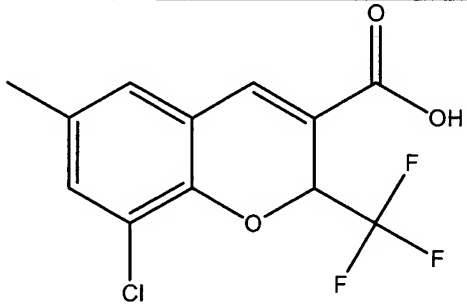
Compound	Name and/or Structure (COX 2 Inhibitor)
B-31	 2-trifluoromethyl-3H-naphtho[2,1-b]pyran-3-carboxylic acid;
B-32	 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-33	 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

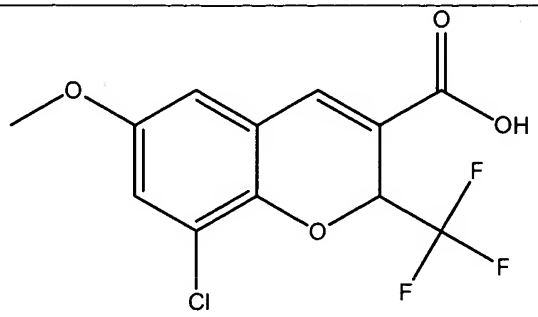
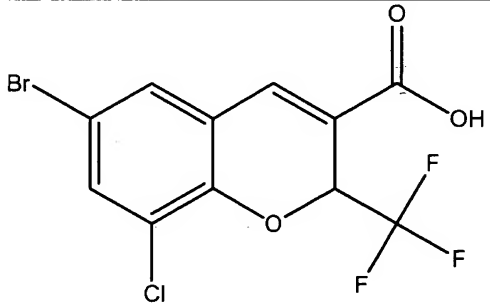
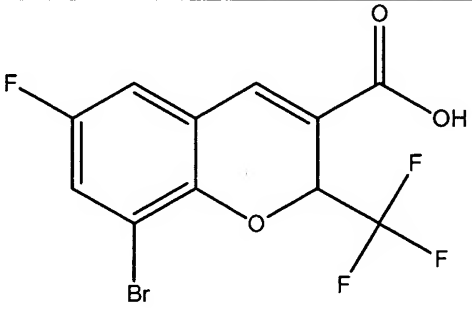
Compound	Name and/or Structure (COX 2 Inhibitor)
B-34	 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-35	 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-36	 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

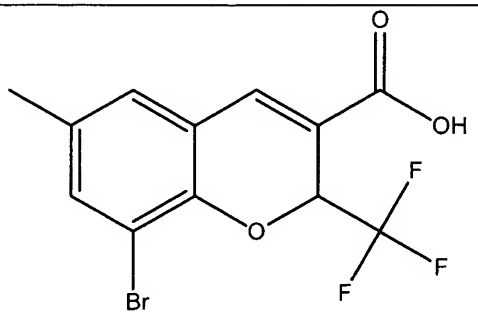
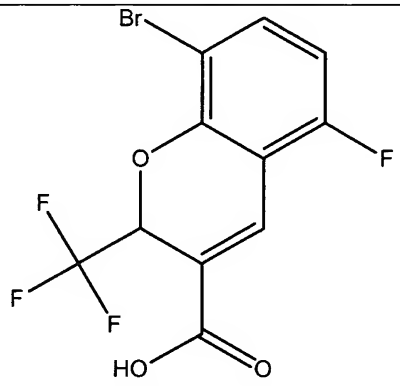
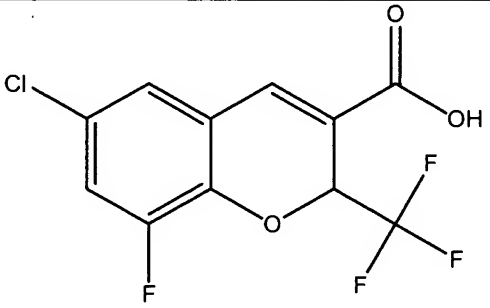
Compound	Name and/or Structure (COX 2 Inhibitor)
B-37	 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-38	 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-39	 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

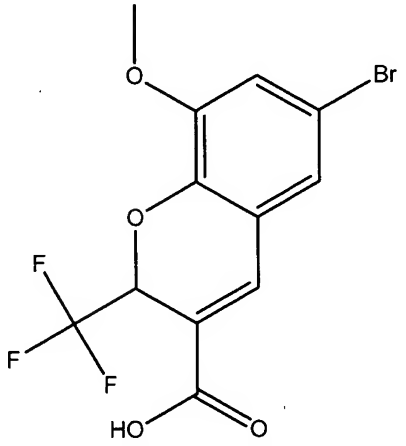
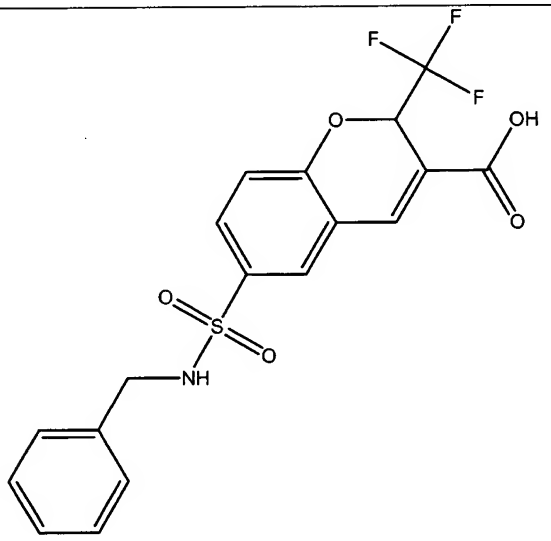
Compound	Name and/or Structure (COX 2 Inhibitor)
B-40	 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-41	 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-42	 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

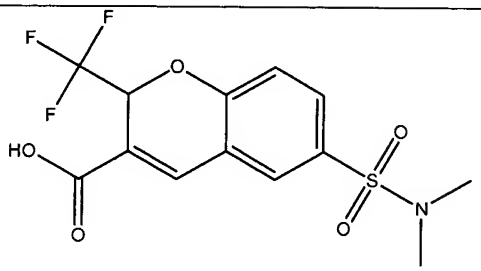
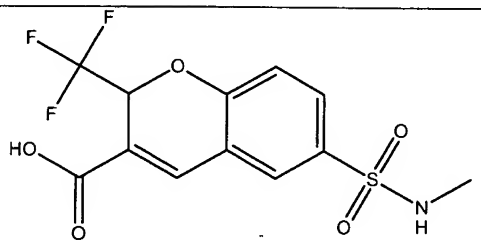
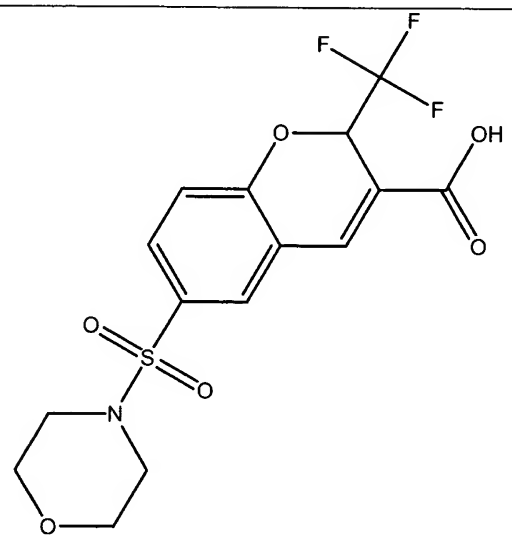
Compound	Name and/or Structure (COX 2 Inhibitor)
B-43	 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-44	 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-45	 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

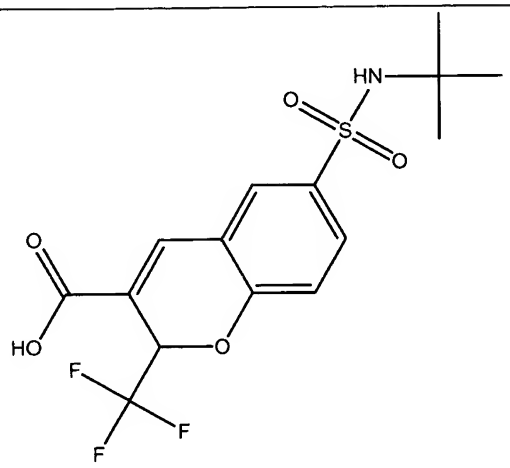
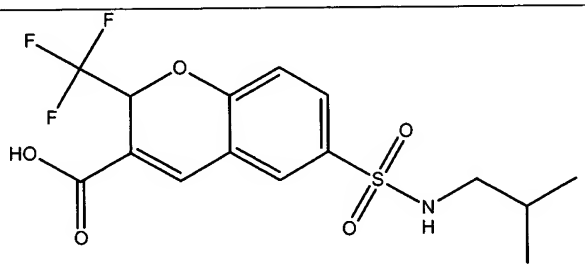
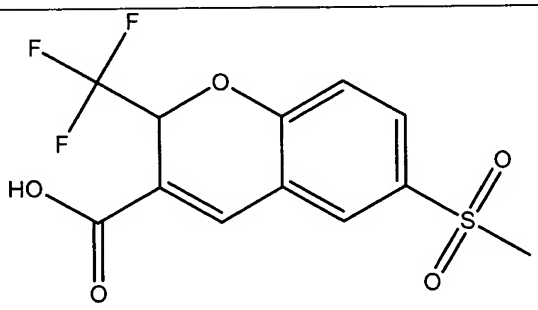
Compound	Name and/or Structure (COX 2 Inhibitor)
B-46	 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-47	 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-48	 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

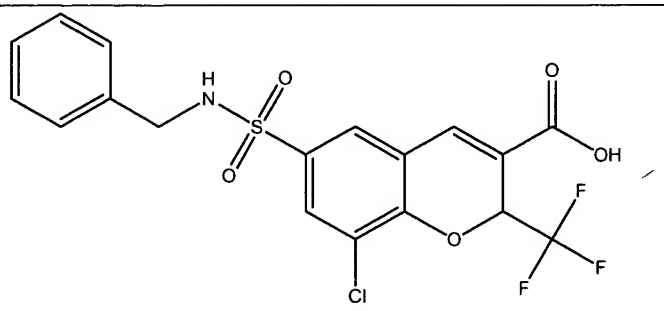
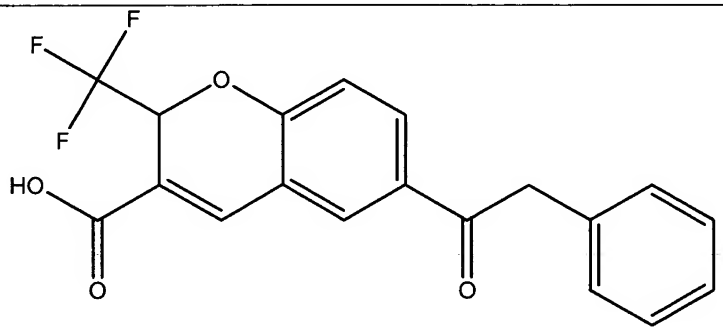
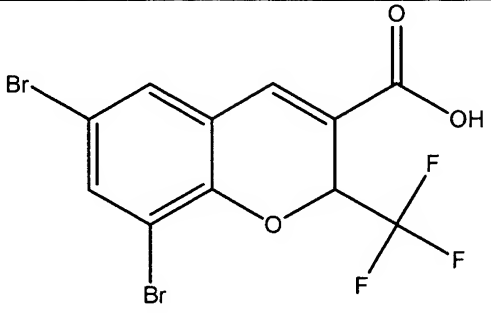
Compound	Name and/or Structure (COX 2 Inhibitor)
B-49	 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-50	 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-51	 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

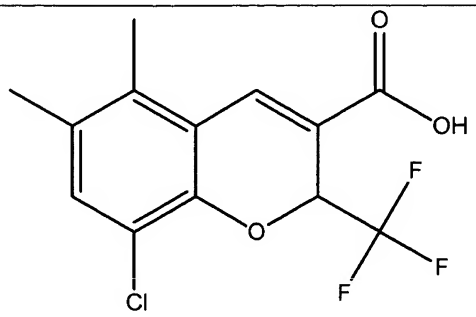
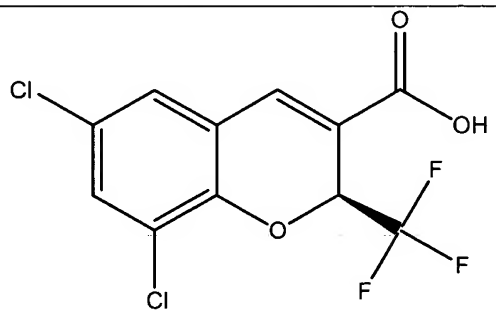
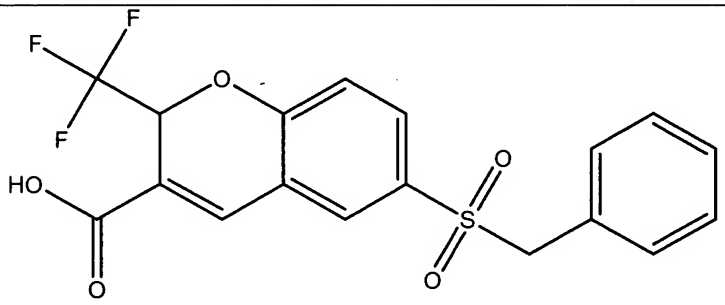
Compound	Name and/or Structure (COX 2 Inhibitor)
B-52	 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-53	 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-54	 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

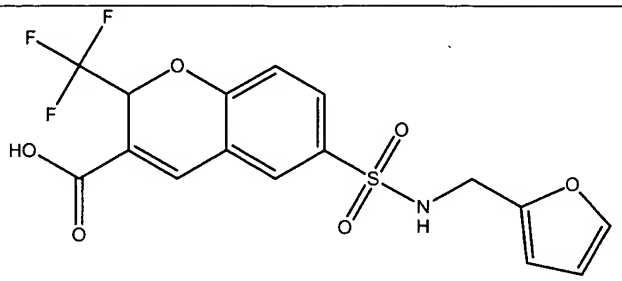
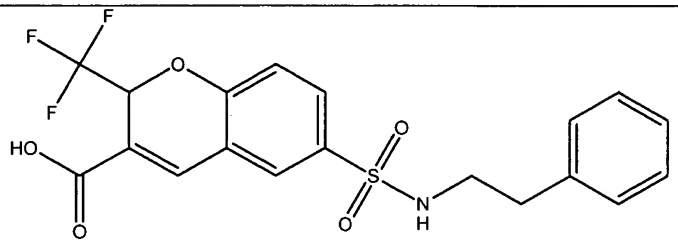
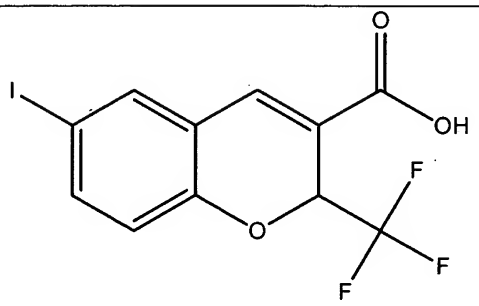
Compound	Name and/or Structure (COX 2 Inhibitor)
B-55	 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-56	 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

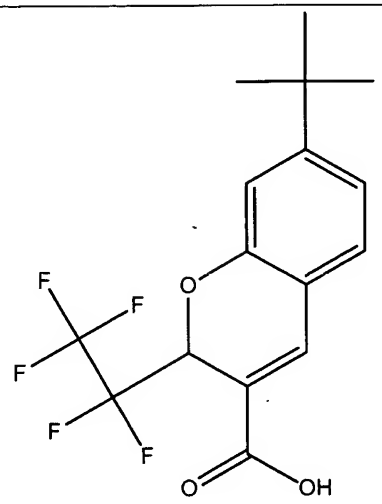
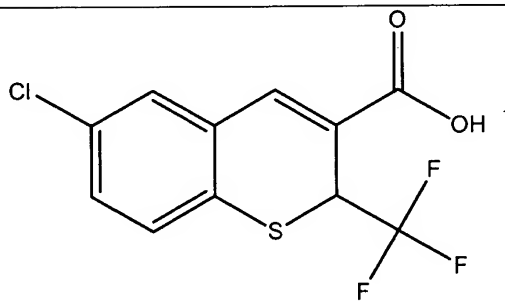
Compound	Name and/or Structure (COX 2 Inhibitor)
B-57	 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-58	 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-59	 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

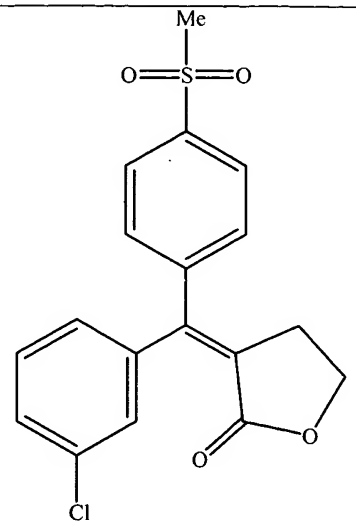
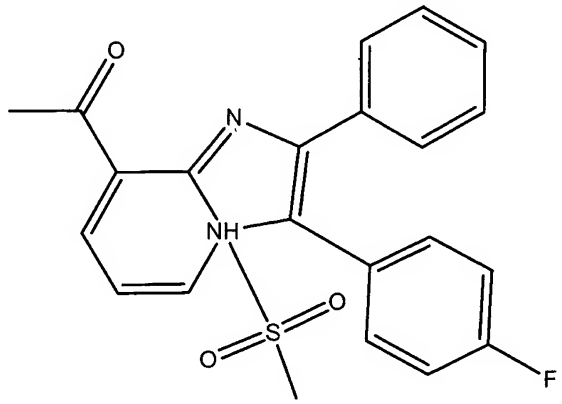
Compound	Name and/or Structure (COX 2 Inhibitor)
B-60	 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-61	 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-62	 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

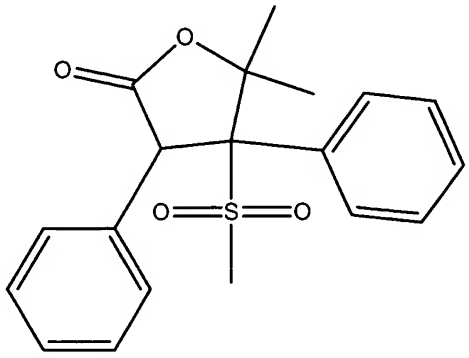
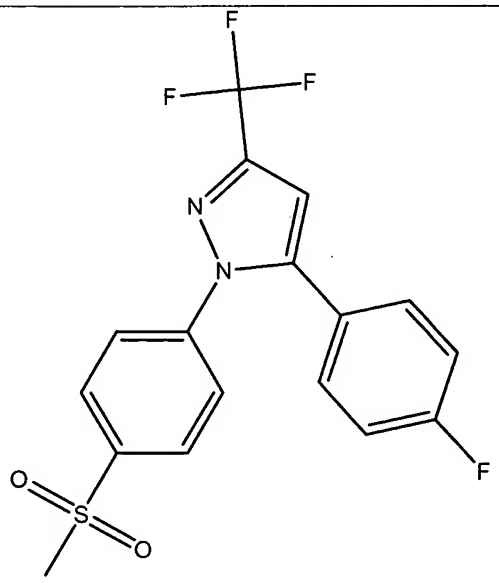
Compound	Name and/or Structure (COX 2 Inhibitor)
B-63	 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-64	 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-65	 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

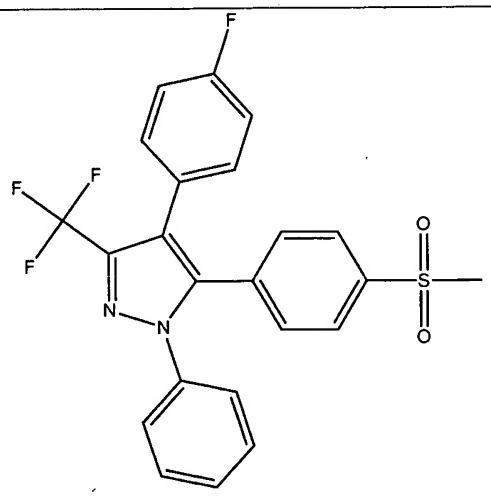
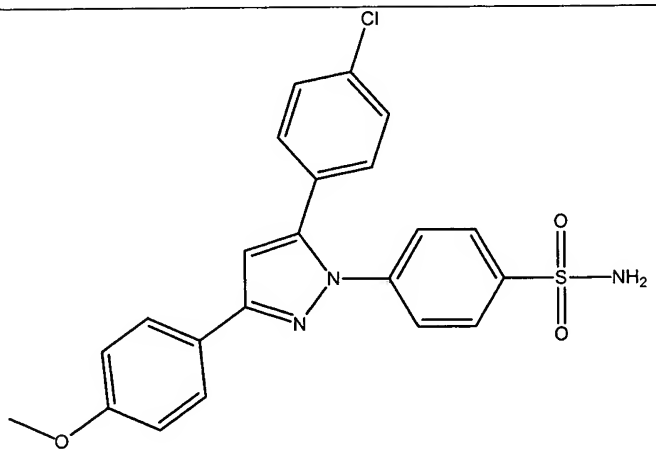
Compound	Name and/or Structure (COX 2 Inhibitor)
B-66	 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-67	 6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-68	 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

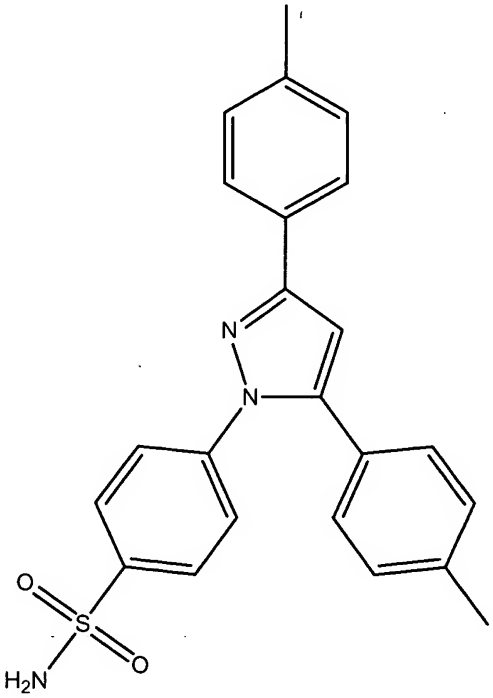
Compound	Name and/or Structure (COX 2 Inhibitor)
B-69	 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-70	 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-71	 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

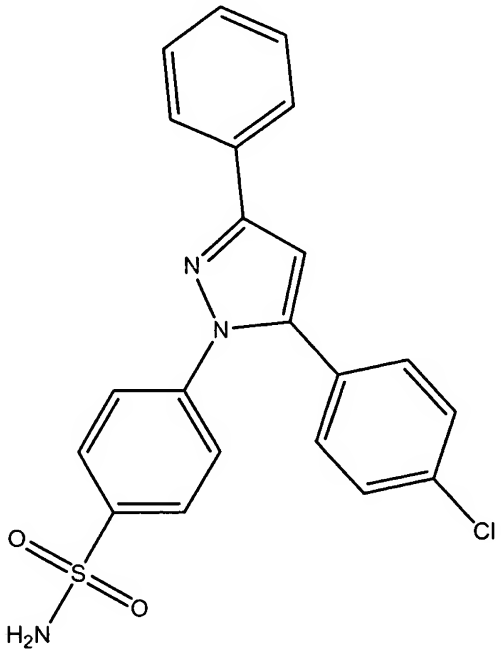
Compound	Name and/or Structure (COX 2 Inhibitor)
B-72	 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;
B-73	 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

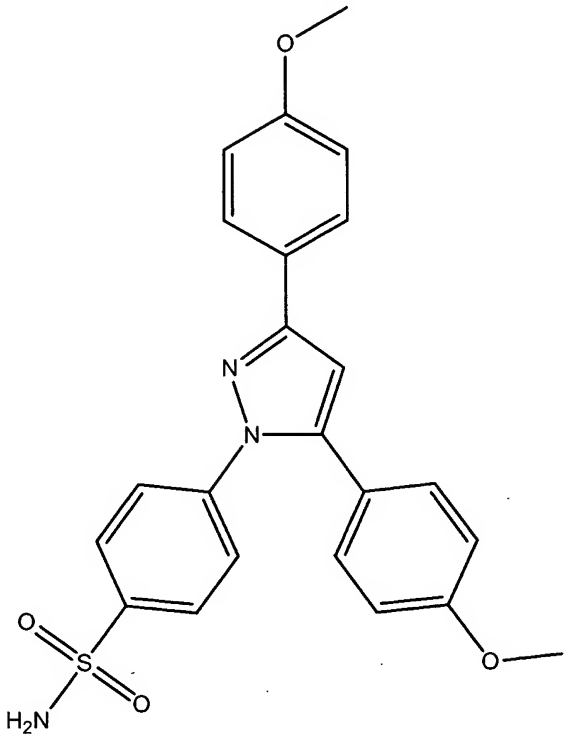
Compound	Name and/or Structure (COX 2 Inhibitor)
B-74	 3-[(3-Chloro-phenyl)-(4-methanesulfonyl-phenyl)-methylene]-dihydro-furan-2-one or BMS-347070;
B-75	 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;

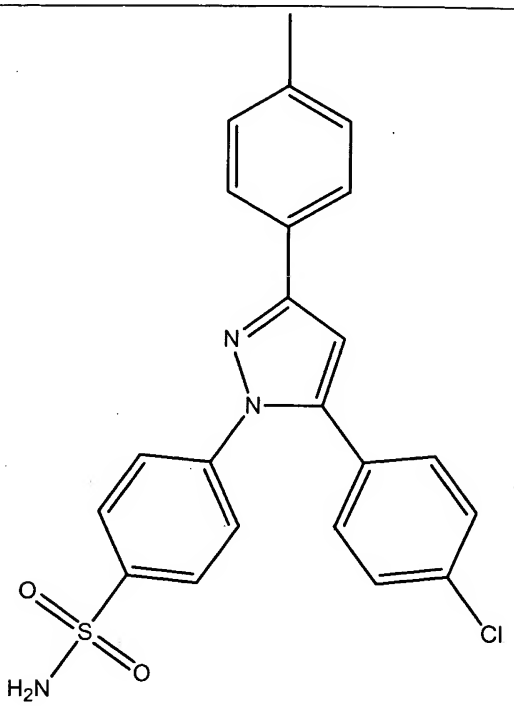
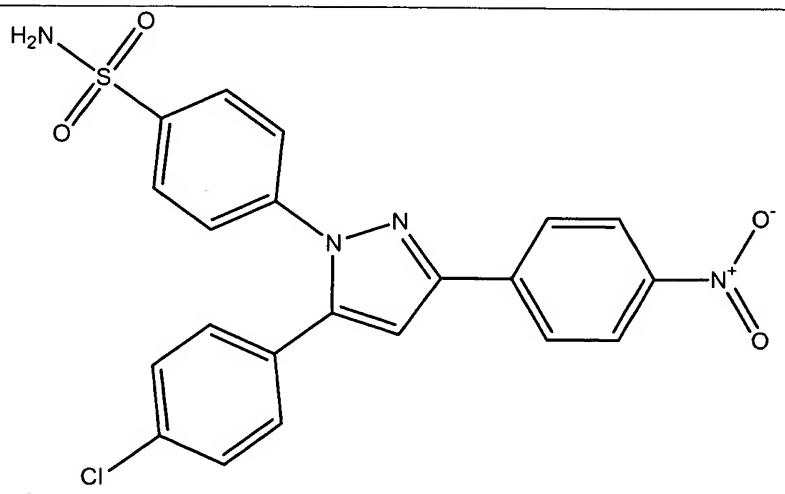
Compound	Name and/or Structure (COX 2 Inhibitor)
B-76	 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;
B-77	 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

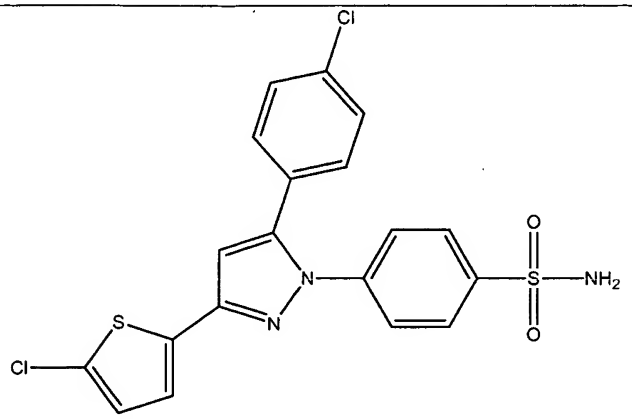
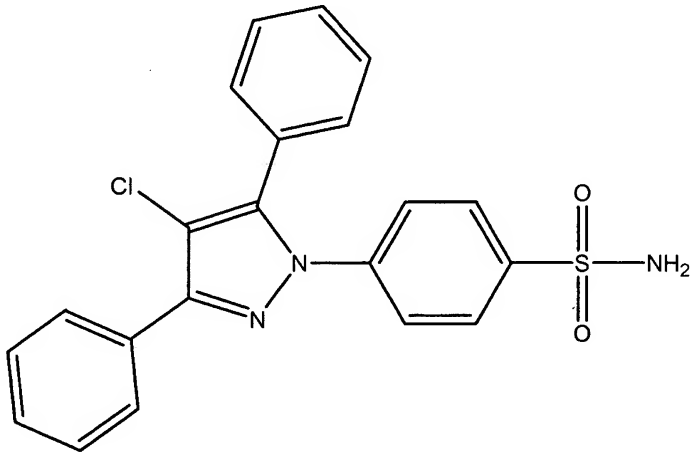
Compound	Name and/or Structure (COX 2 Inhibitor)
B-78	 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;
B-79	 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

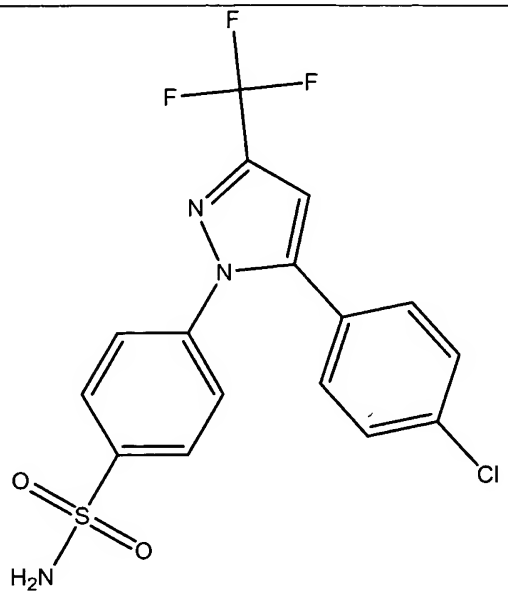
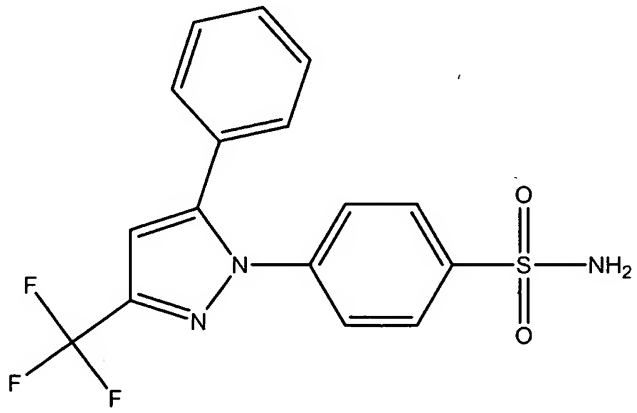
Compound	Name and/or Structure (COX 2 Inhibitor)
B-80	 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

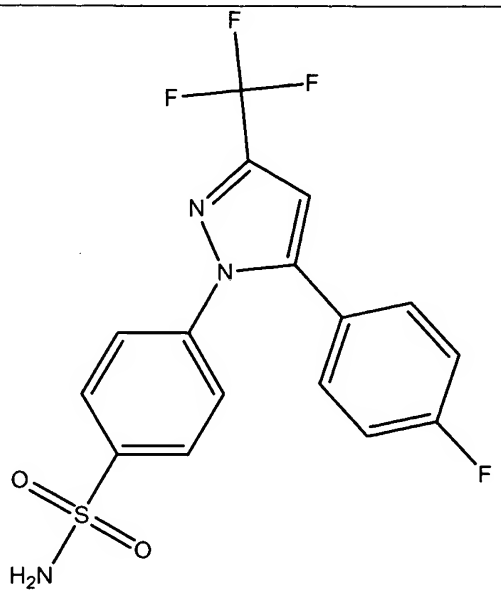
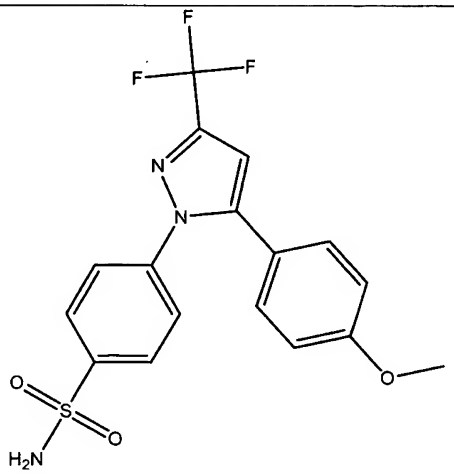
Compound	Name and/or Structure (COX 2 Inhibitor)
B-81	 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

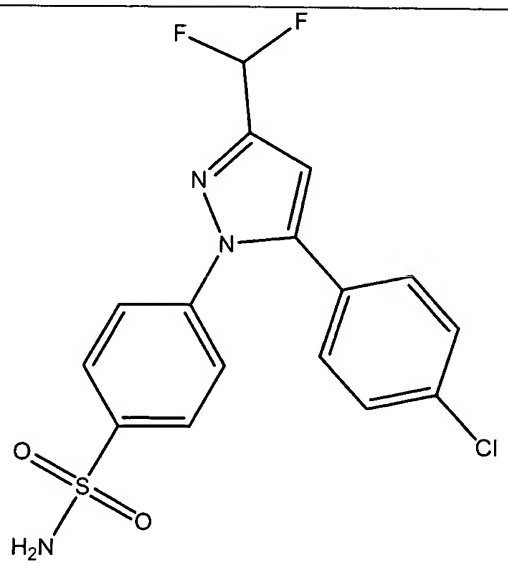
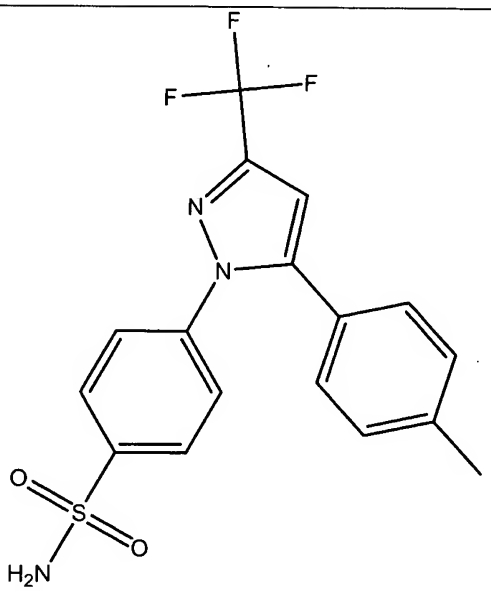
Compound	Name and/or Structure (COX 2 Inhibitor)
B-82	 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

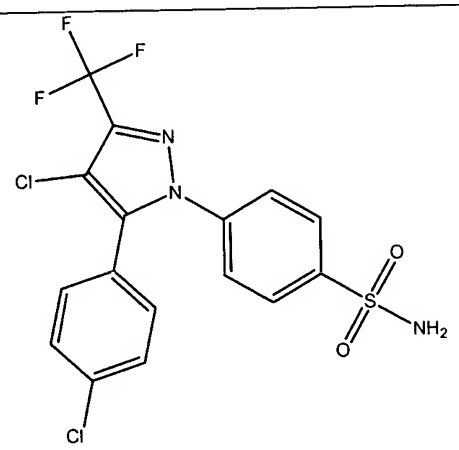
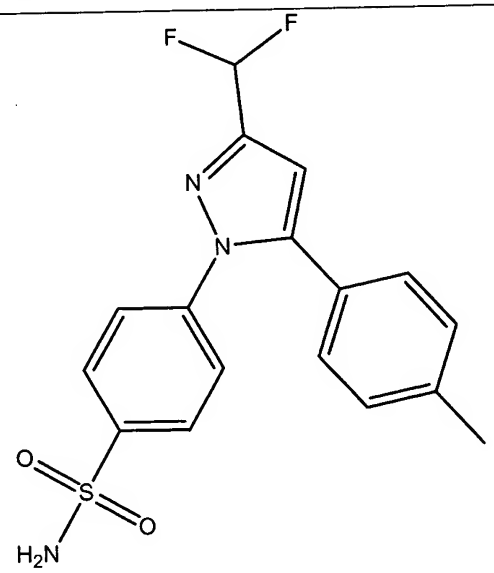
Compound	Name and/or Structure (COX 2 Inhibitor)
B-83	 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-84	 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

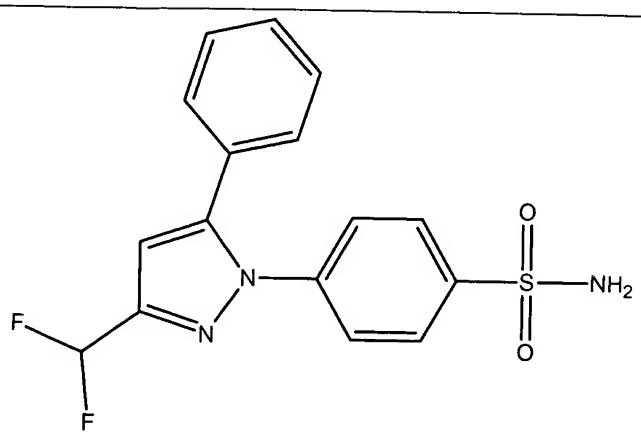
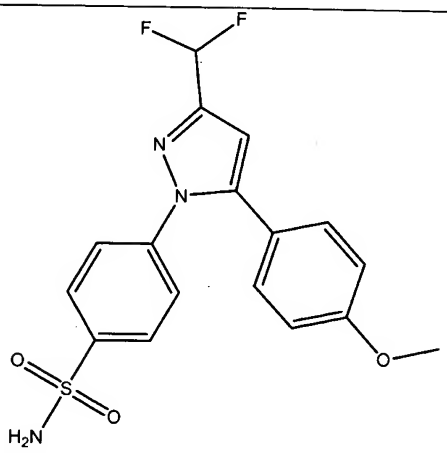
Compound	Name and/or Structure (COX 2 Inhibitor)
B-85	 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;
B-86	 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide;

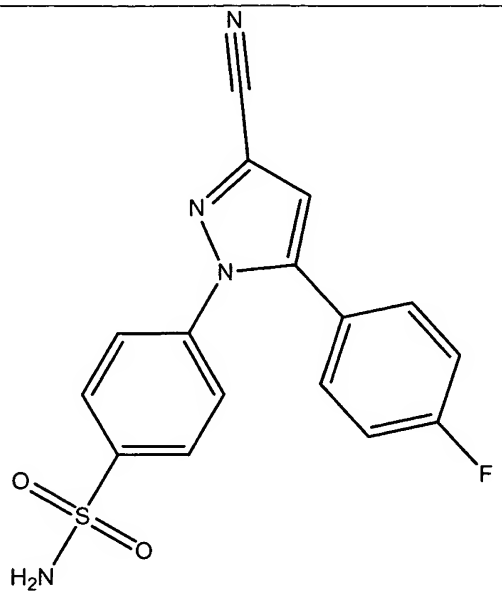
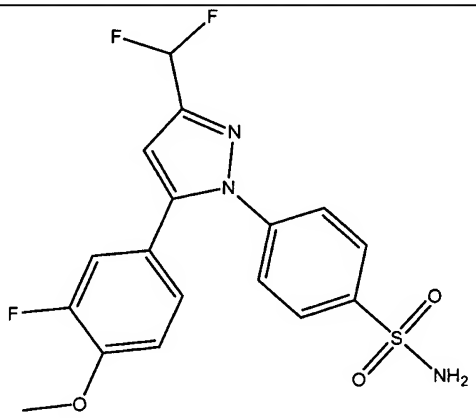
Compound	Name and/or Structure (COX 2 Inhibitor)
B-87	 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-88	 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

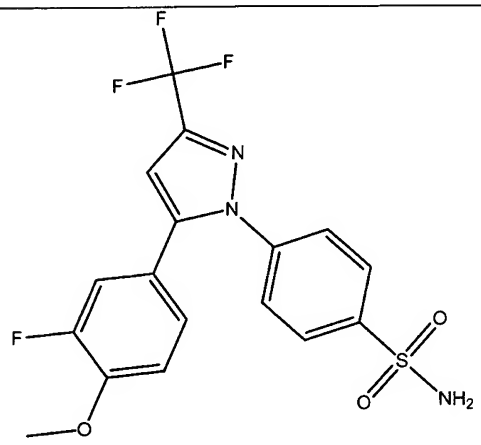
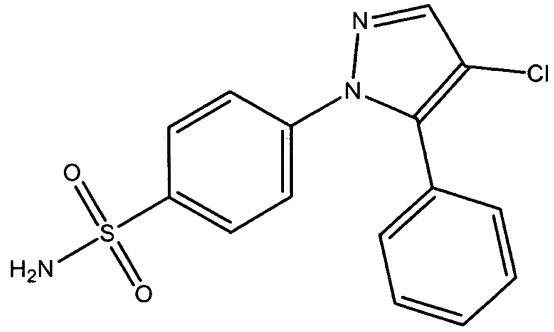
Compound	Name and/or Structure (COX 2 Inhibitor)
B-89	 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-90	 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

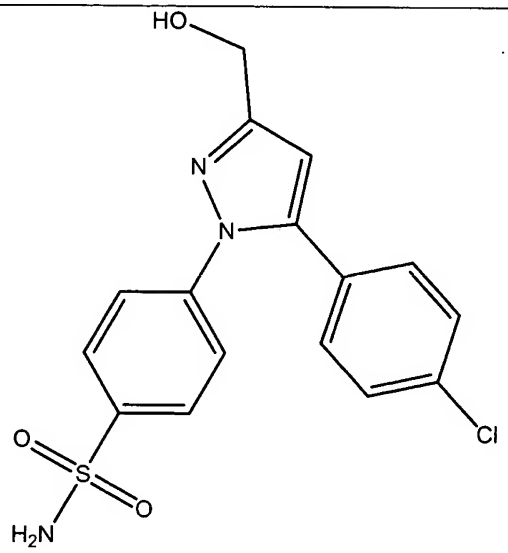
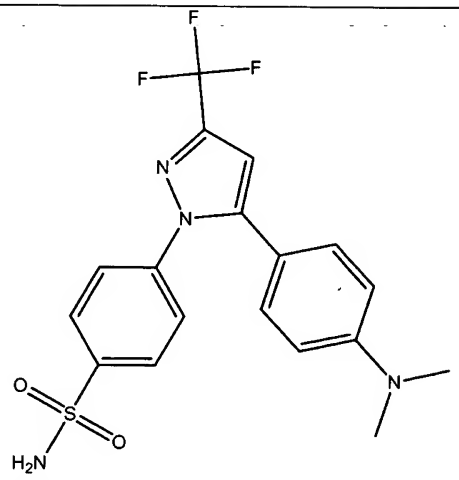
Compound	Name and/or Structure (COX 2 Inhibitor)
B-91	 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-92	 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

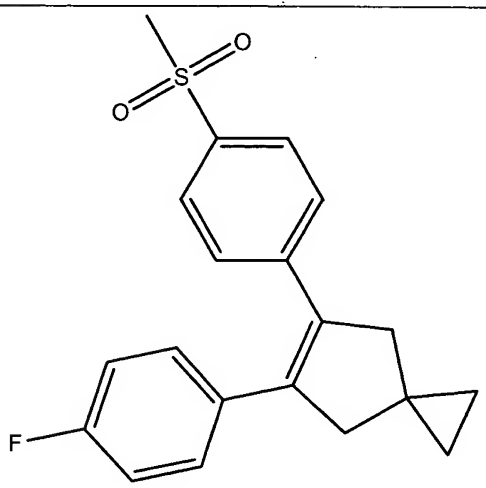
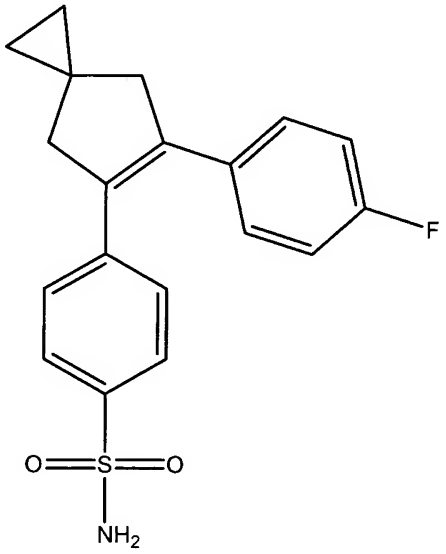
Compound	Name and/or Structure (COX 2 Inhibitor)
B-93	 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-94	 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

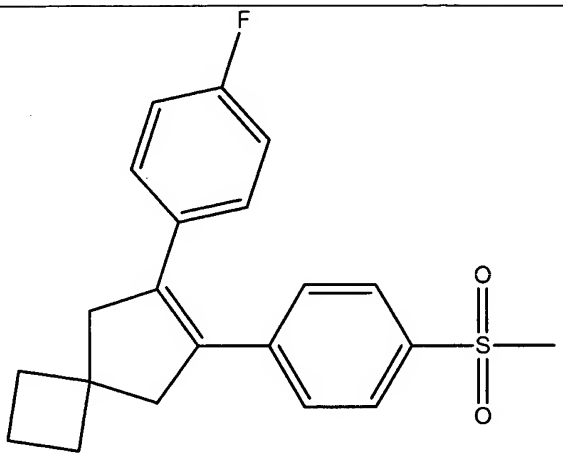
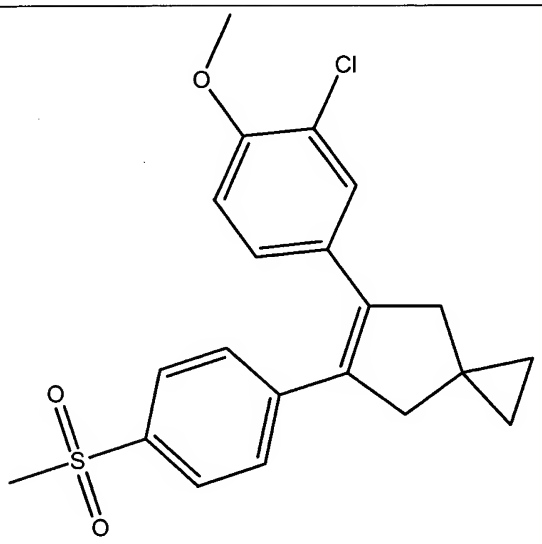
Compound	Name and/or Structure (COX 2 Inhibitor)
B-95	 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;
B-96	 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

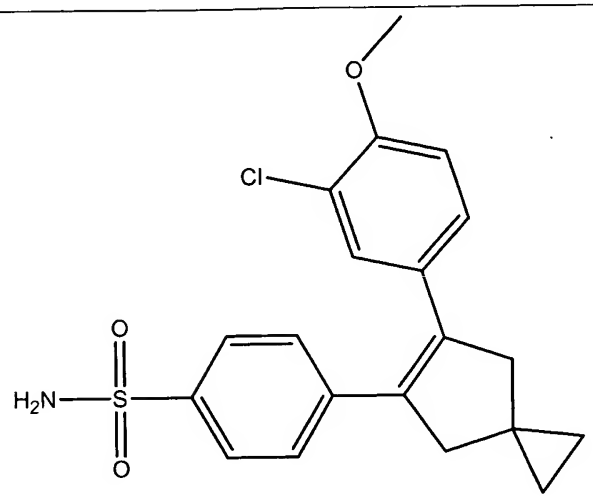
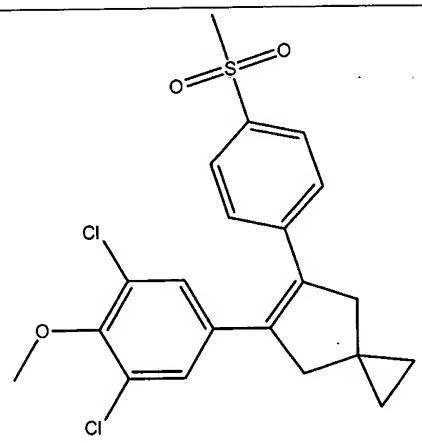
Compound	Name and/or Structure (COX 2 Inhibitor)
B-97	 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-98	 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

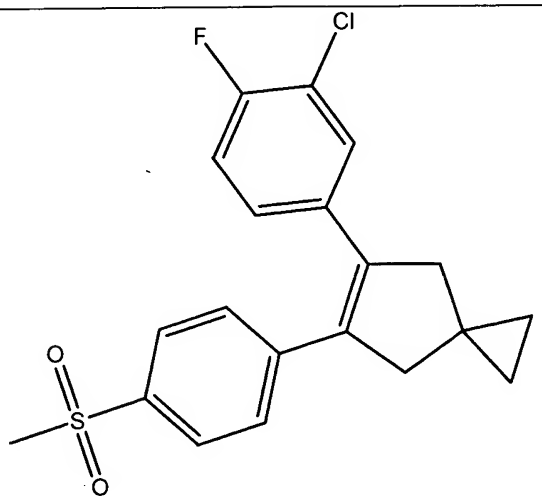
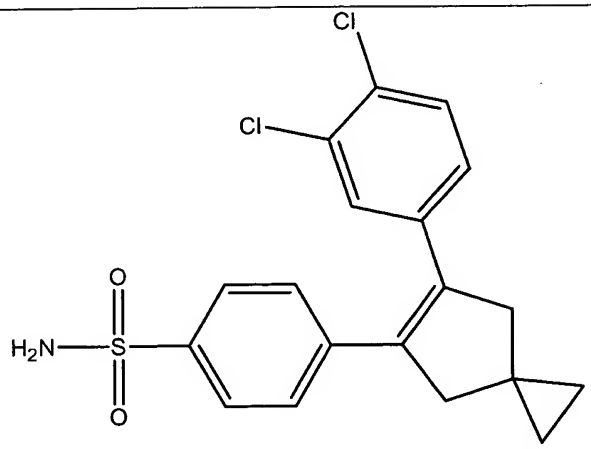
Compound	Name and/or Structure (COX 2 Inhibitor)
B-99	 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-100	 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

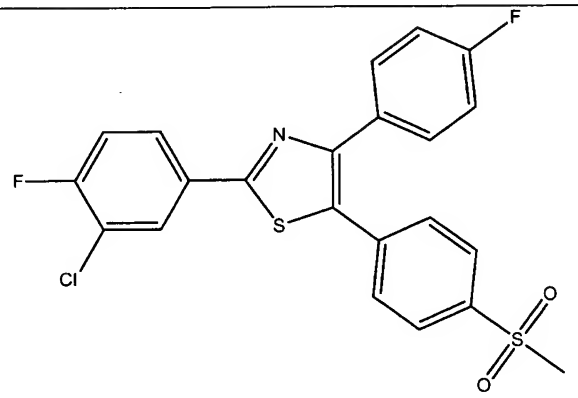
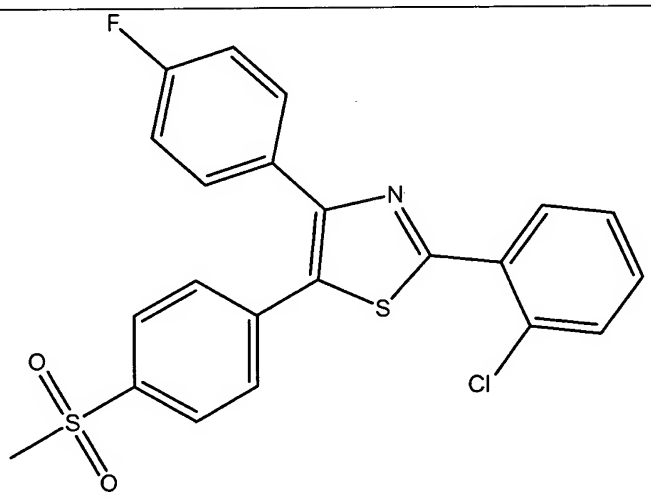
Compound	Name and/or Structure (COX 2 Inhibitor)
B-101	 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-102	 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

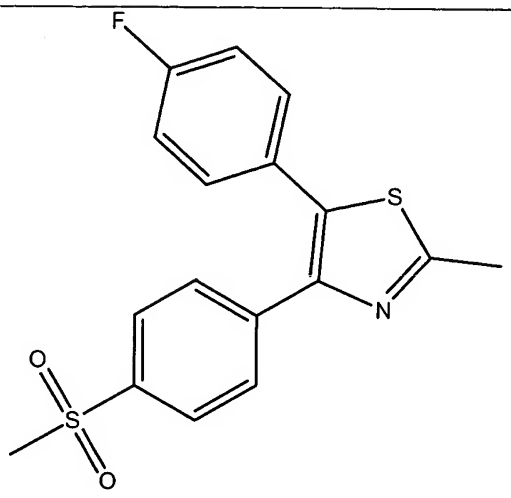
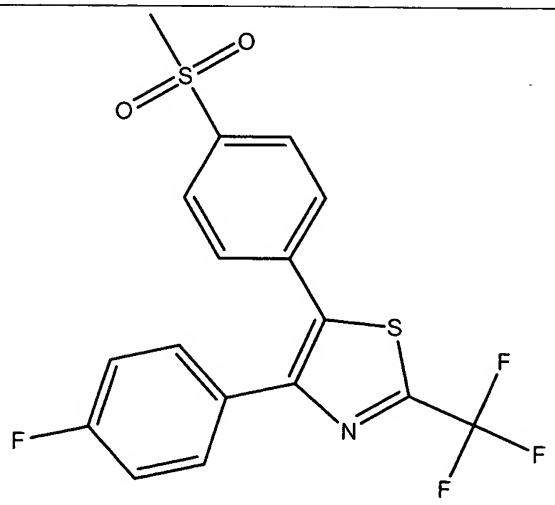
Compound	Name and/or Structure (COX 2 Inhibitor)
B-103	 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-104	 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

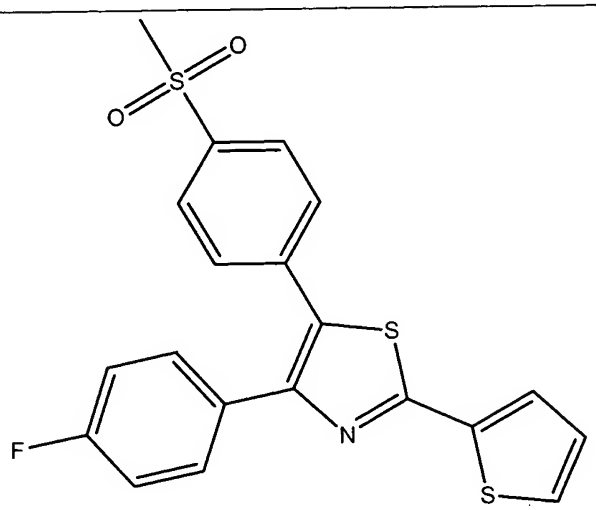
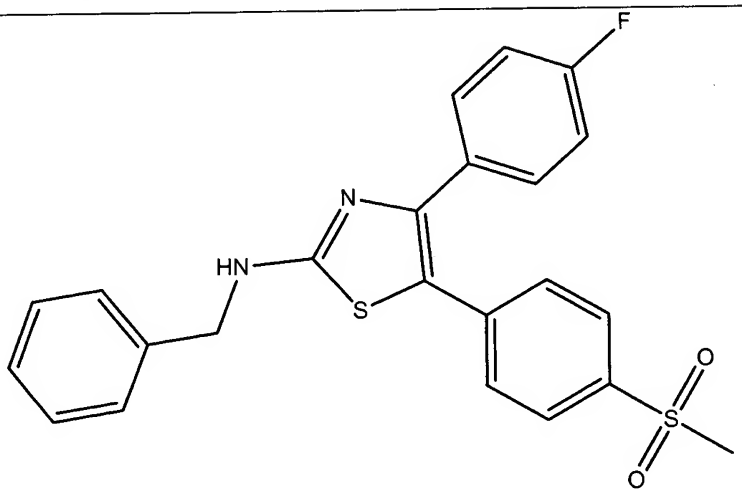
Compound	Name and/or Structure (COX 2 Inhibitor)
B-105	 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;
B-106	 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

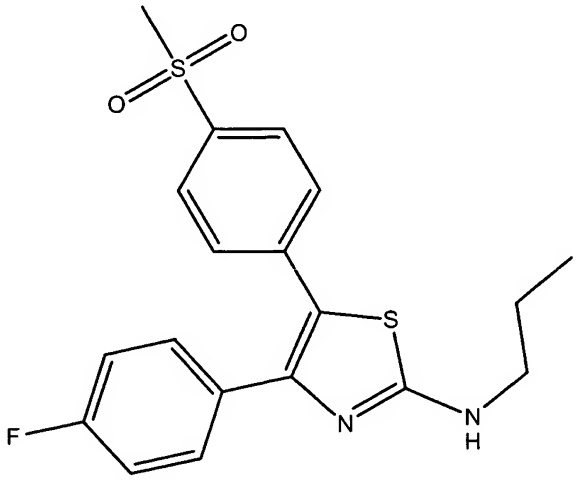
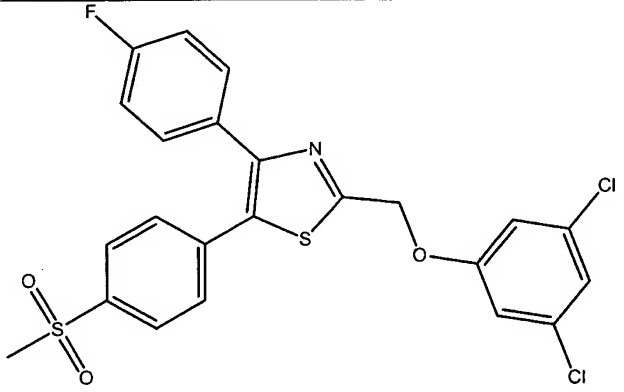
Compound	Name and/or Structure (COX 2 Inhibitor)
B-107	 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;
B-108	 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

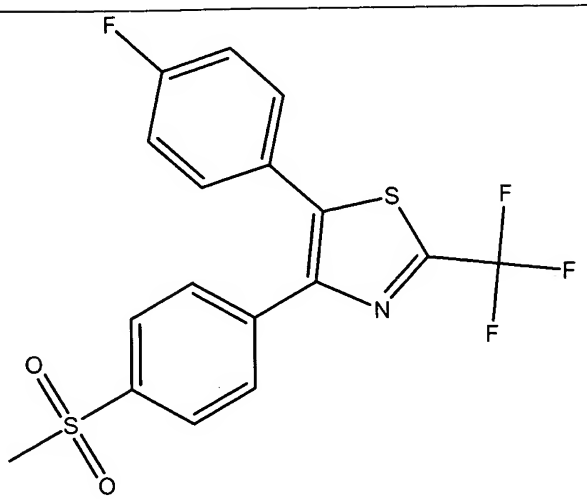
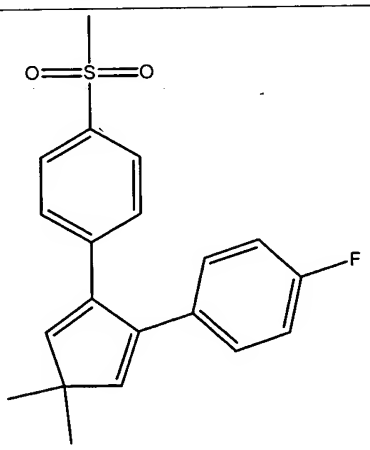
Compound	Name and/or Structure (COX 2 Inhibitor)
B-109	 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;
B-110	 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

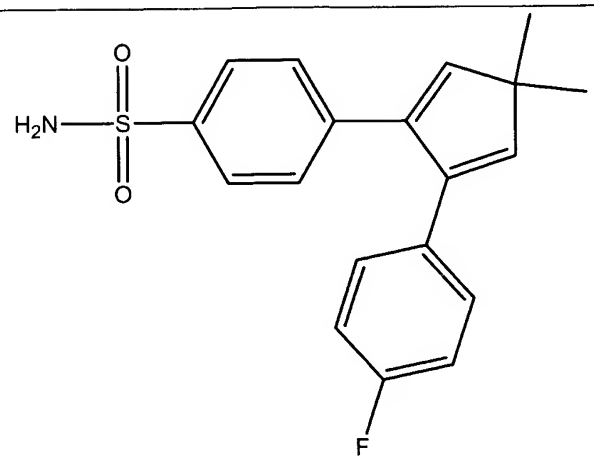
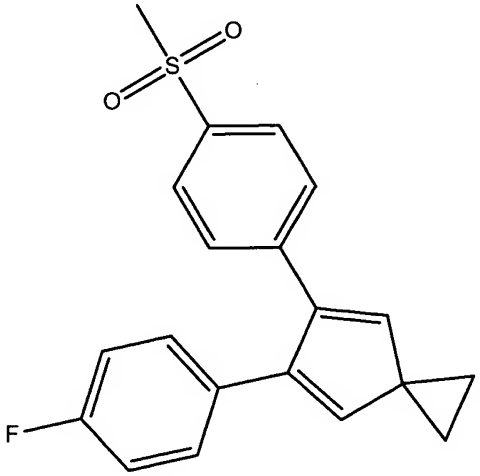
Compound	Name and/or Structure (COX 2 Inhibitor)
B-111	 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;
B-112	 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

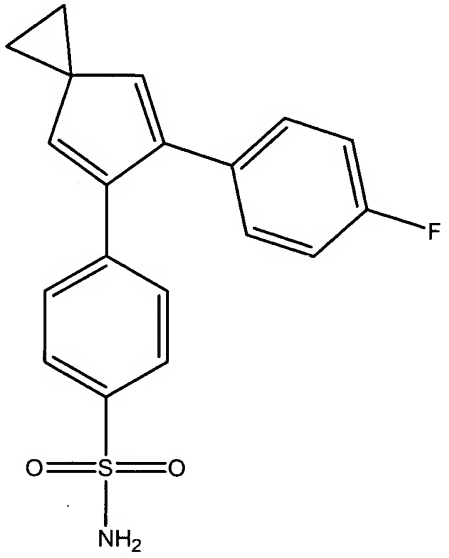
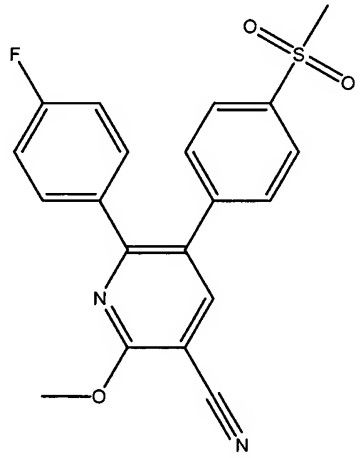
Compound	Name and/or Structure (COX 2 Inhibitor)
B-113	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;
B-114	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

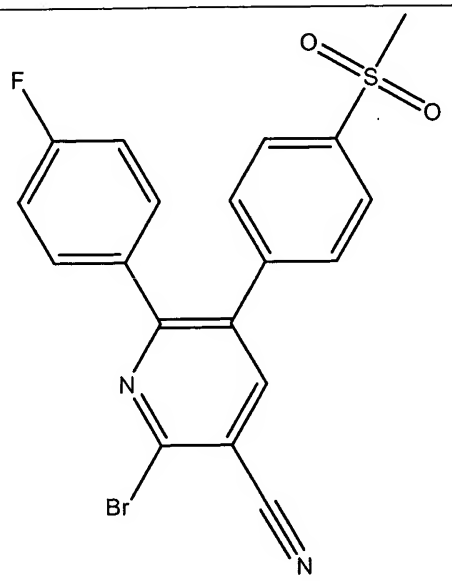
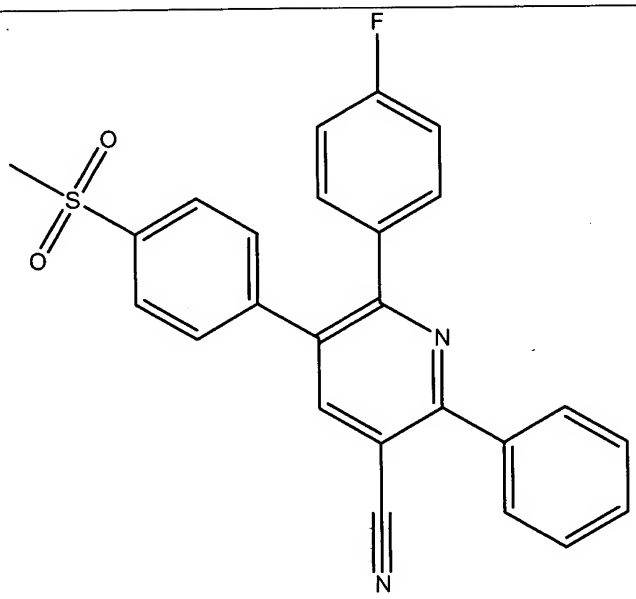
Compound	Name and/or Structure (COX 2 Inhibitor)
B-115	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;
B-116	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

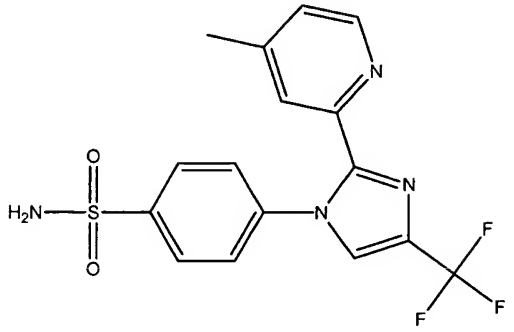
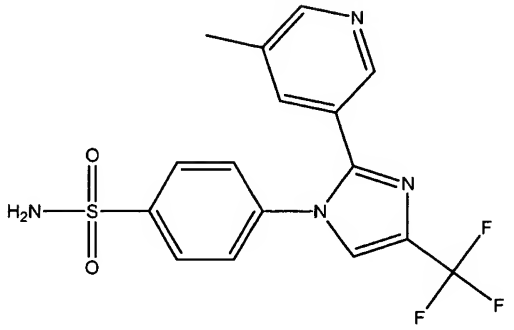
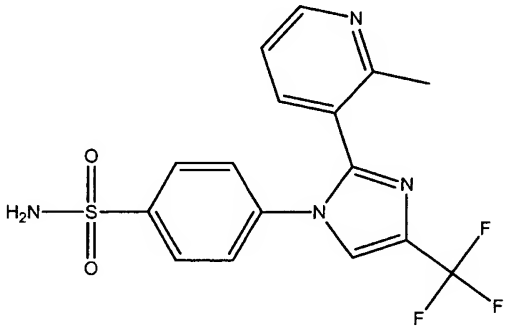
Compound	Name and/or Structure (COX 2 Inhibitor)
B-117	 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;
B-118	 2-((3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

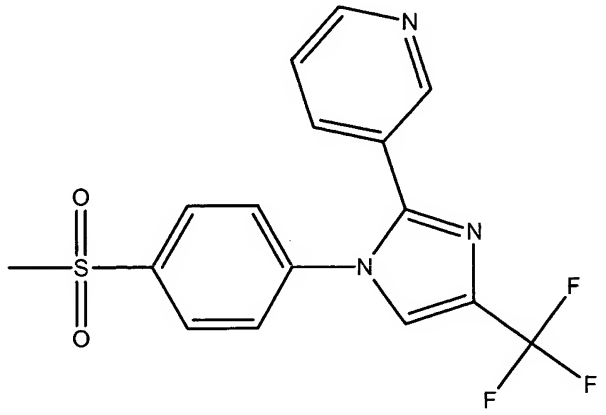
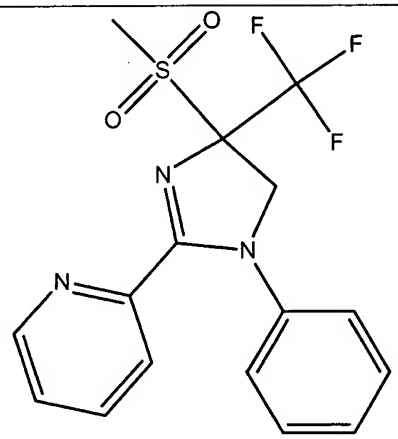
Compound	Name and/or Structure (COX 2 Inhibitor)
B-119	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;
B-120	 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;

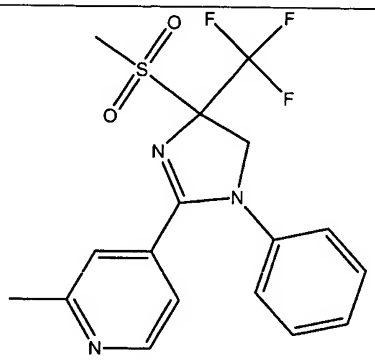
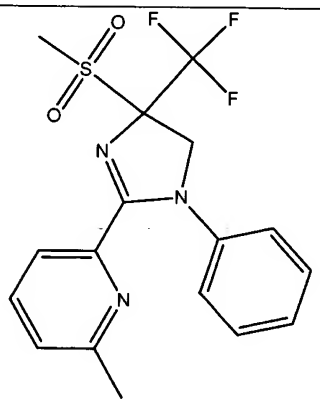
Compound	Name and/or Structure (COX 2 Inhibitor)
B-121	 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;
B-122	 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;

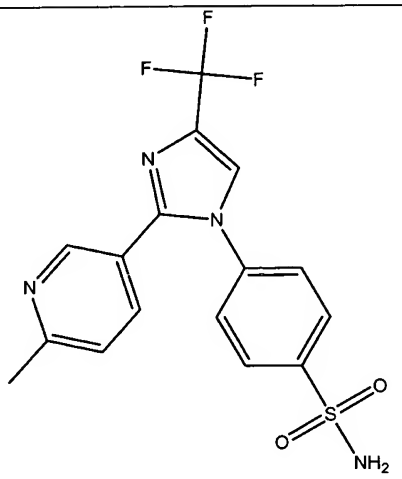
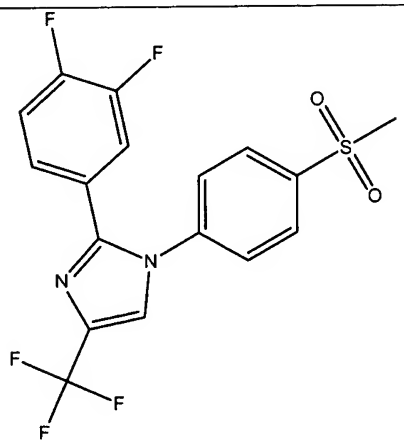
Compound	Name and/or Structure (COX 2 Inhibitor)
B-123	 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;
B-124	 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

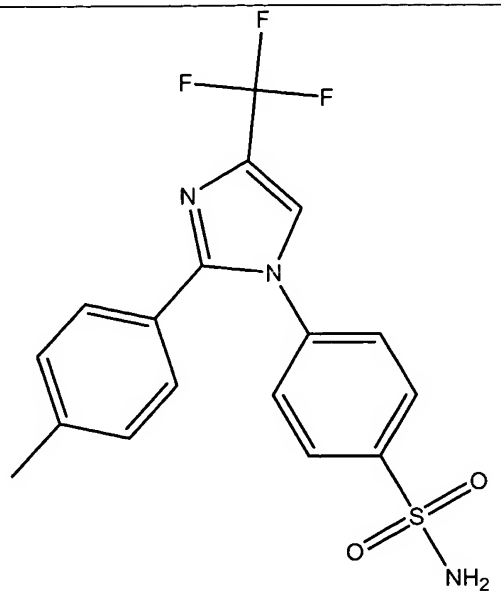
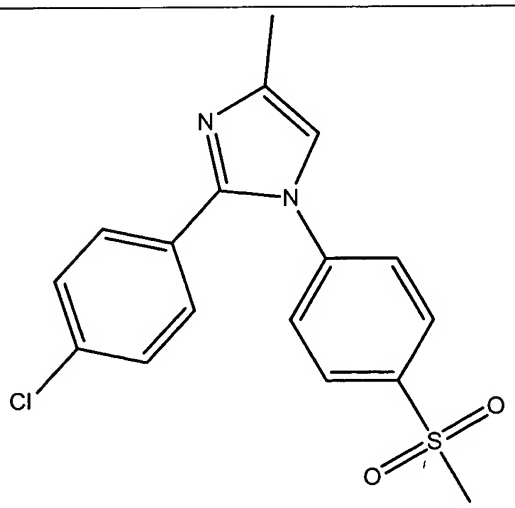
Compound	Name and/or Structure (COX 2 Inhibitor)
B-125	 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;
B-126	 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;

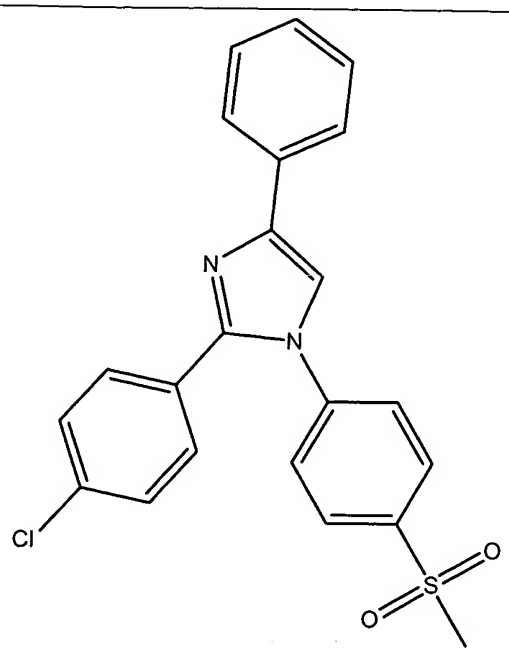
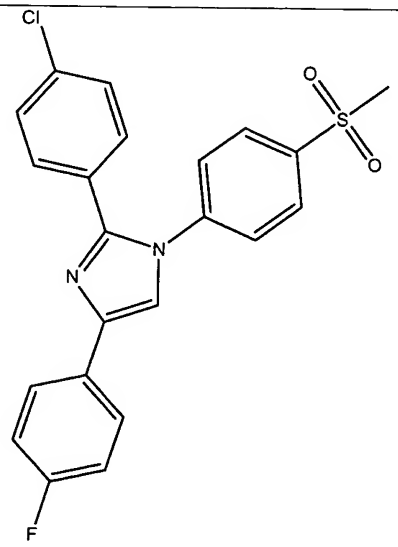
Compound	Name and/or Structure (COX 2 Inhibitor)
B-127	 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
B-128	 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
B-129	 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

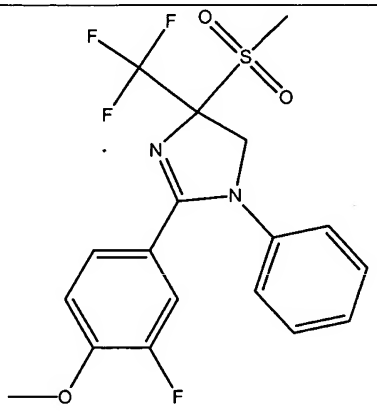
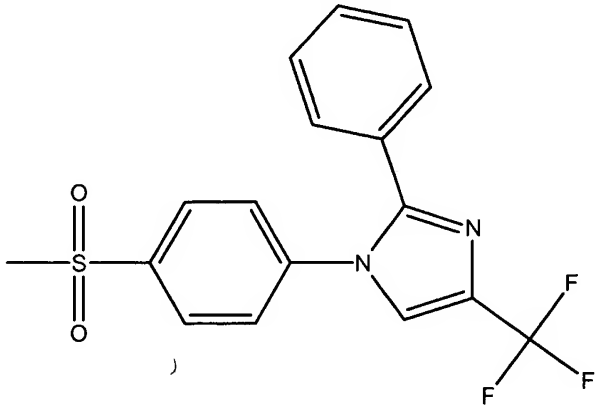
Compound	Name and/or Structure (COX 2 Inhibitor)
B-130	 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;
B-131	 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)]-1H-imidazol-2-yl]pyridine;

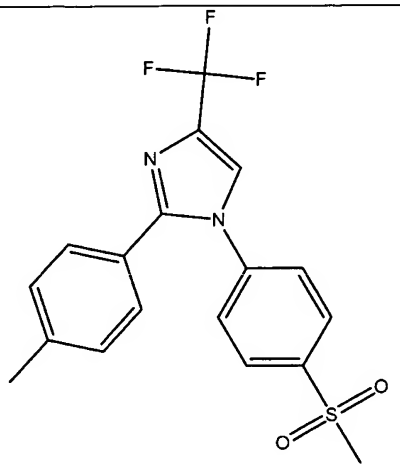
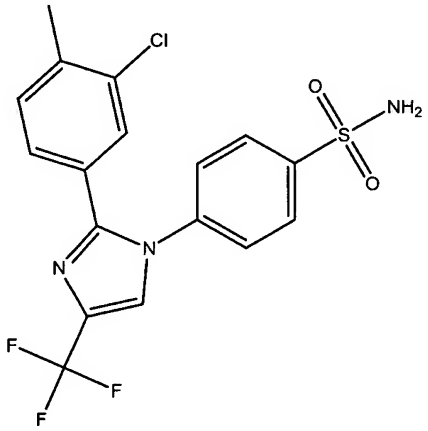
Compound	Name and/or Structure (COX 2 Inhibitor)
B-132	 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)]-1H-imidazol-2-yl]pyridine;
B-133	 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)]-1H-imidazol-2-yl]pyridine;

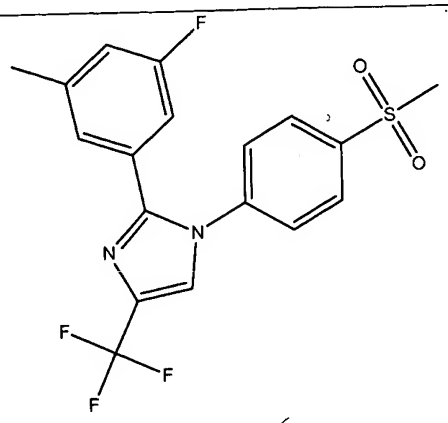
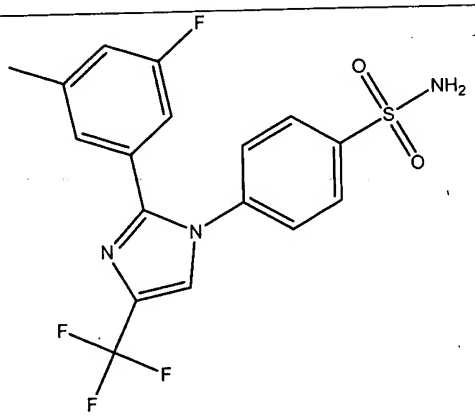
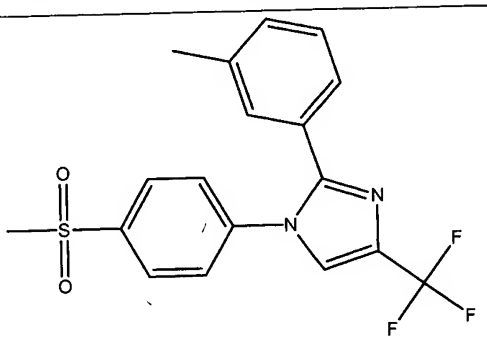
Compound	Name and/or Structure (COX 2 Inhibitor)
B-134	 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
B-135	 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

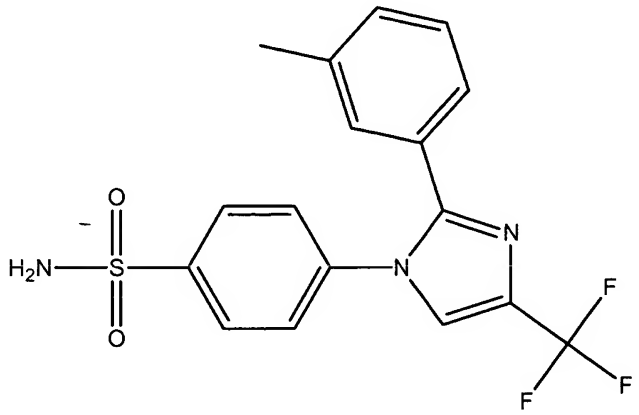
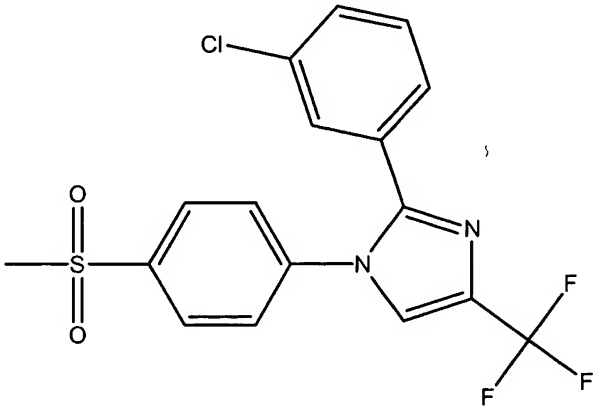
Compound	Name and/or Structure (COX 2 Inhibitor)
B-136	 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
B-137	 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

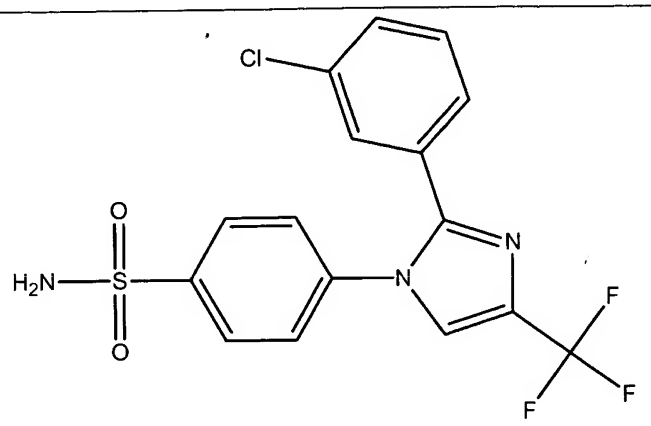
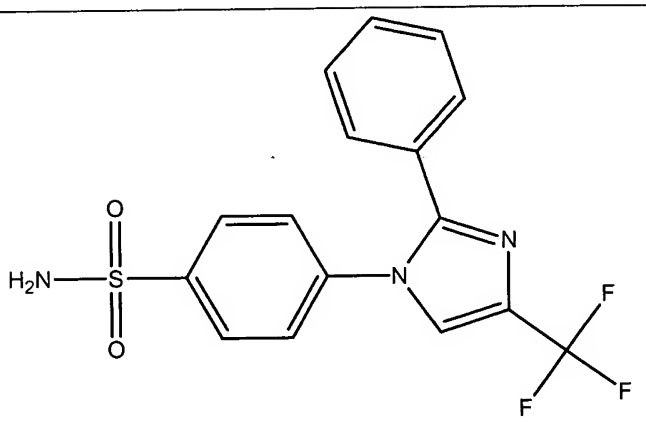
Compound	Name and/or Structure (COX 2 Inhibitor)
B-138	 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;
B-139	 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

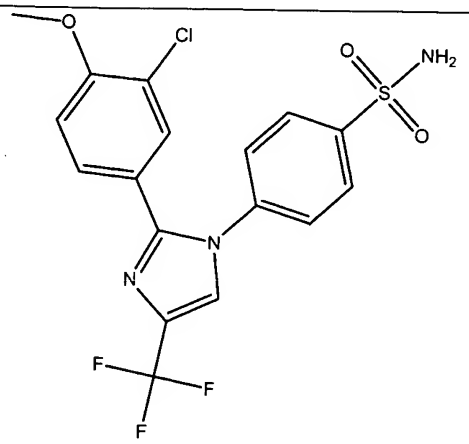
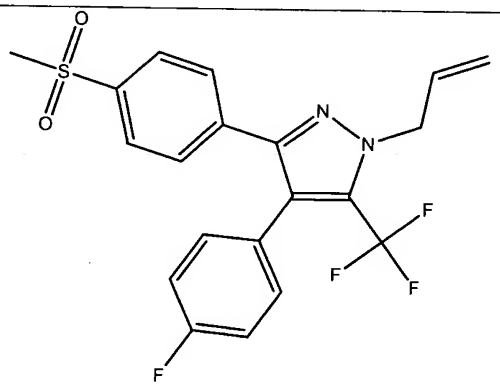
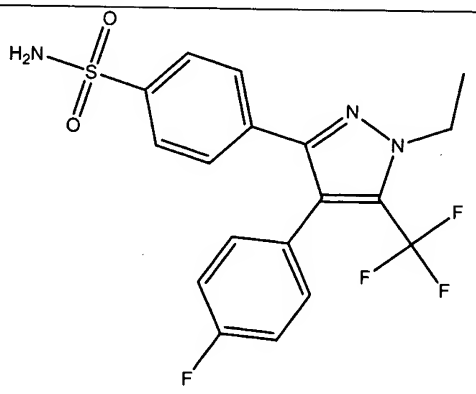
Compound	Name and/or Structure (COX 2 Inhibitor)
B-140	 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)]-1H-imidazole;
B-141	 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;

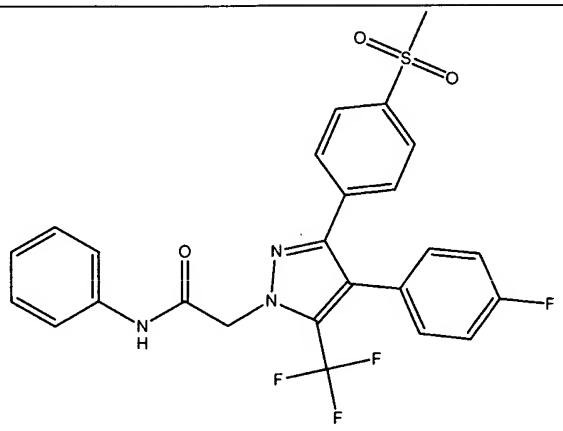
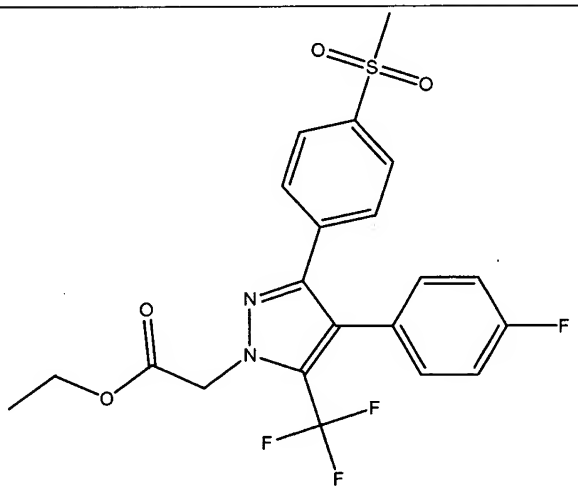
Compound	Name and/or Structure (COX 2 Inhibitor)
B-142	 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;
B-143	 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

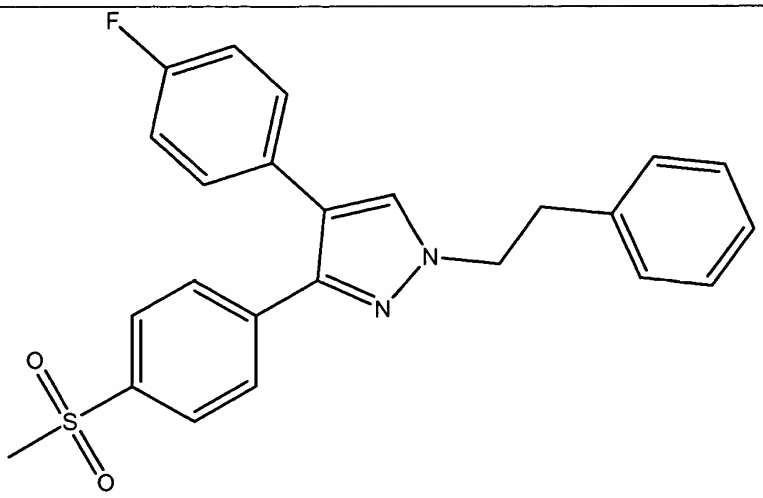
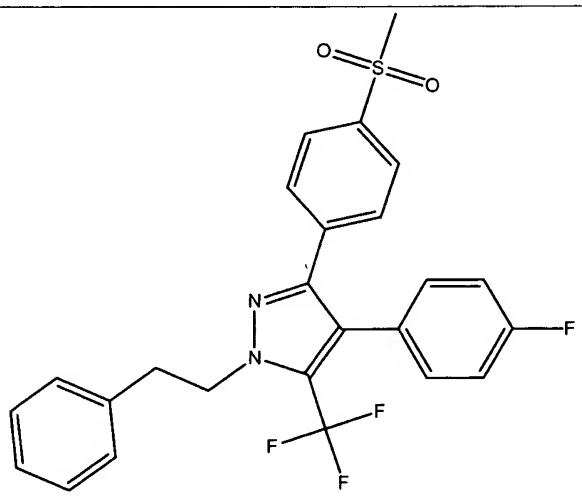
Compound	Name and/or Structure (COX 2 Inhibitor)
B-144	 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;
B-145	 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
B-146	 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

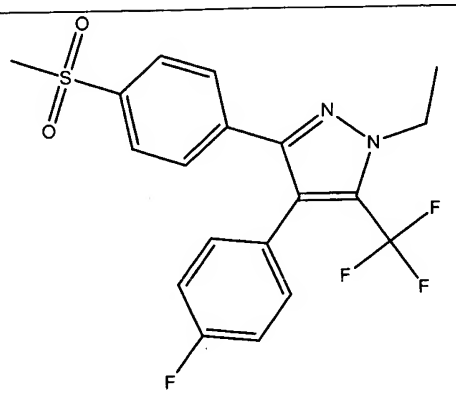
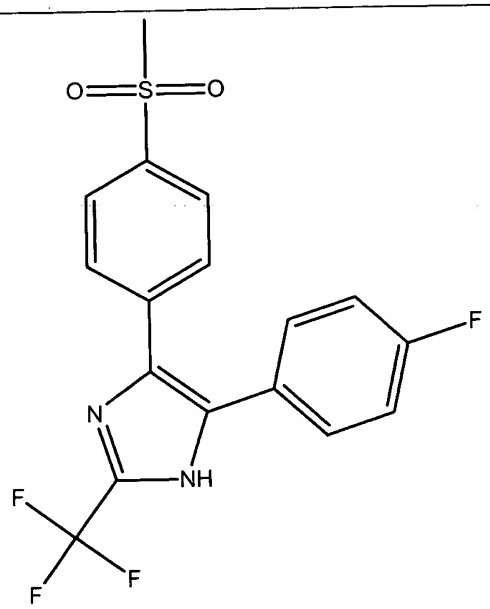
Compound	Name and/or Structure (COX 2 Inhibitor)
B-147	 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-148	 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;

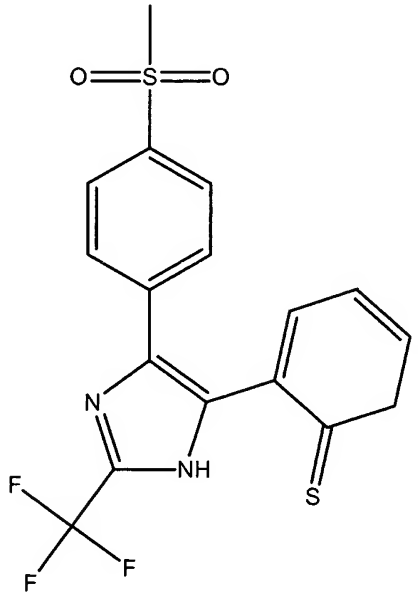
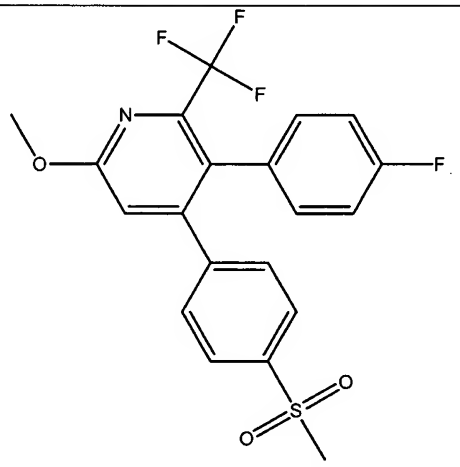
Compound	Name and/or Structure (COX 2 Inhibitor)
B-149	 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-150	 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

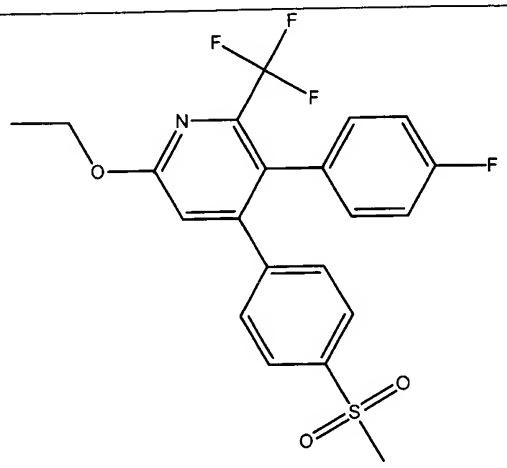
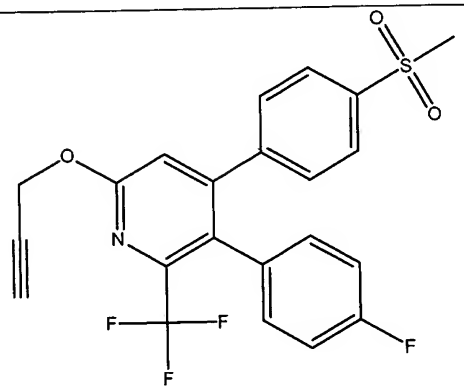
Compound	Name and/or Structure (COX 2 Inhibitor)
B-151	 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;
B-152	 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
B-153	 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;

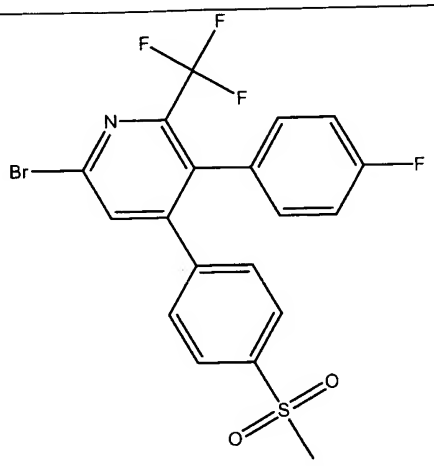
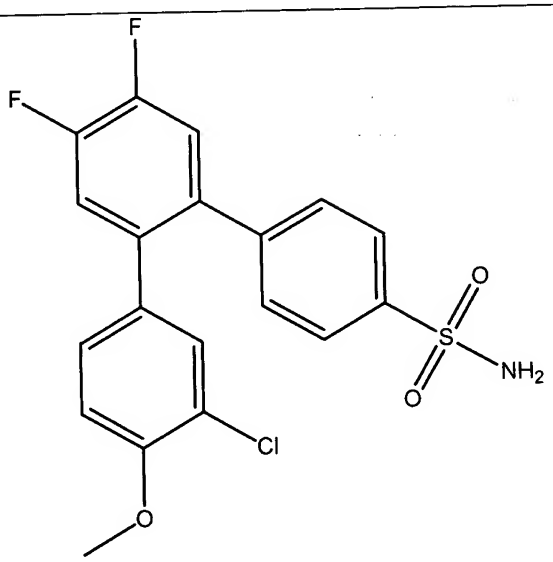
Compound	Name and/or Structure (COX 2 Inhibitor)
B-154	 N-phenyl-[4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;
B-155	 ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

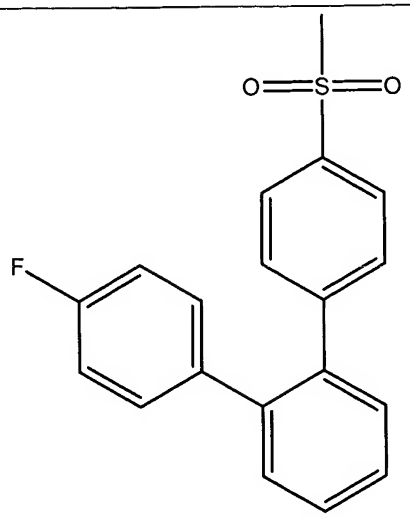
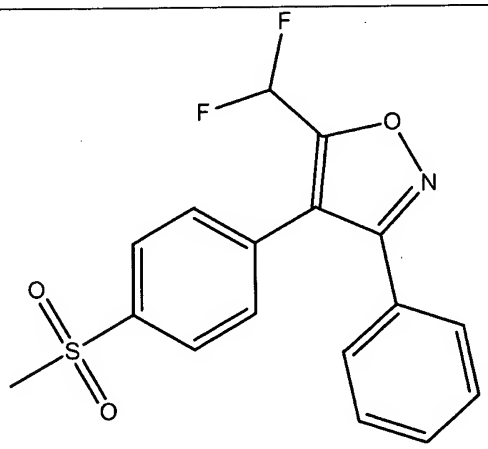
Compound	Name and/or Structure (COX 2 Inhibitor)
B-156	 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;
B-157	 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

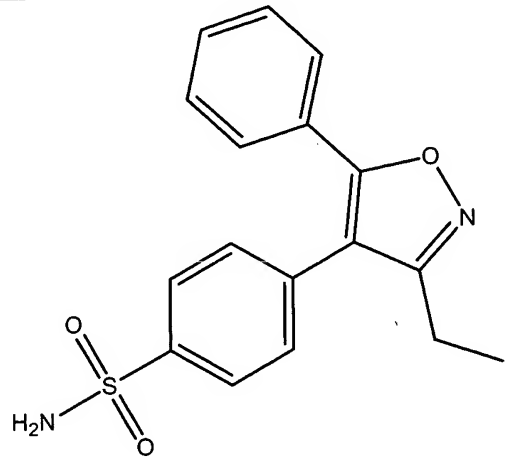
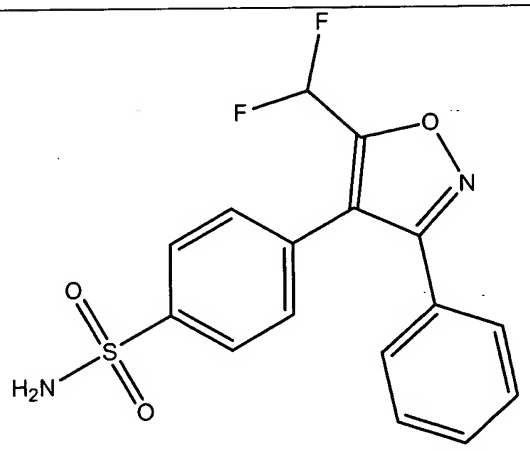
Compound	Name and/or Structure (COX 2 Inhibitor)
B-158	 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;
B-159	 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;

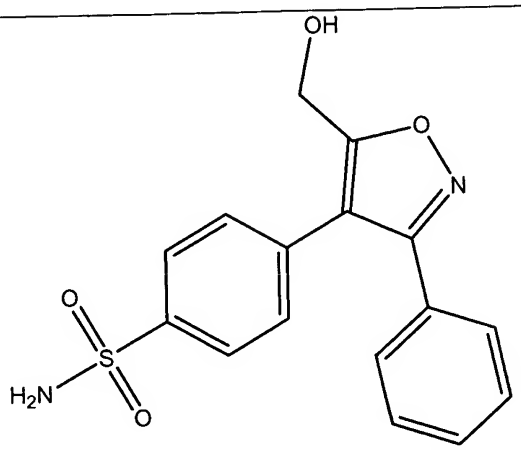
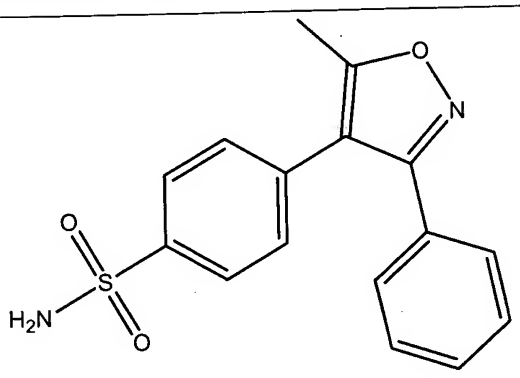
Compound	Name and/or Structure (COX 2 Inhibitor)
B-160	 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;
B-161	 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

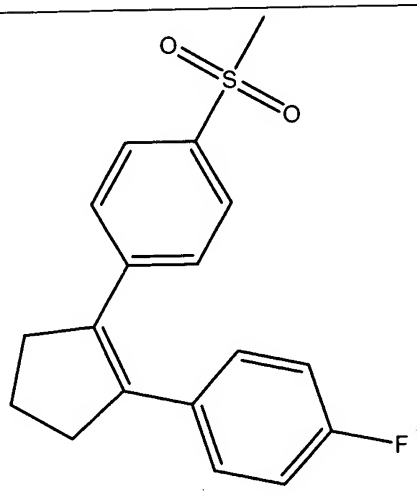
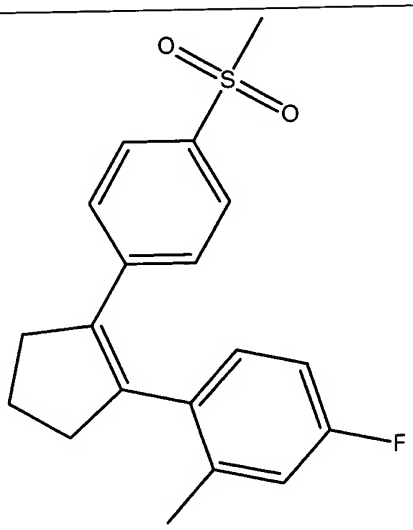
Compound	Name and/or Structure (COX 2 Inhibitor)
B-162	 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
B-163	 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

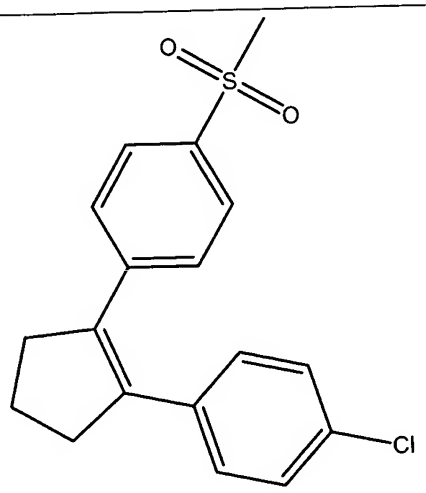
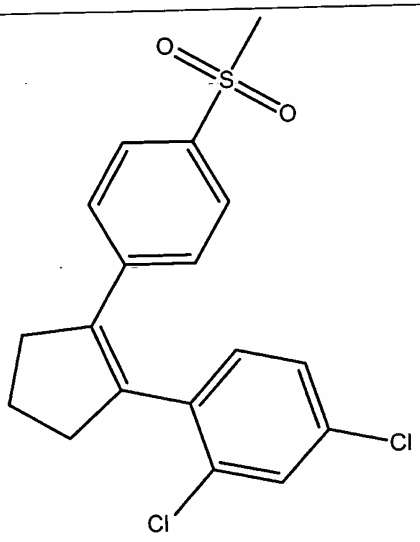
Compound	Name and/or Structure (COX 2 Inhibitor)
B-164	 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;
B-165	 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;

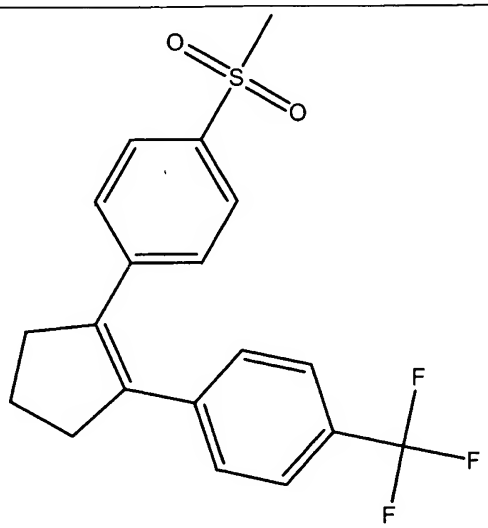
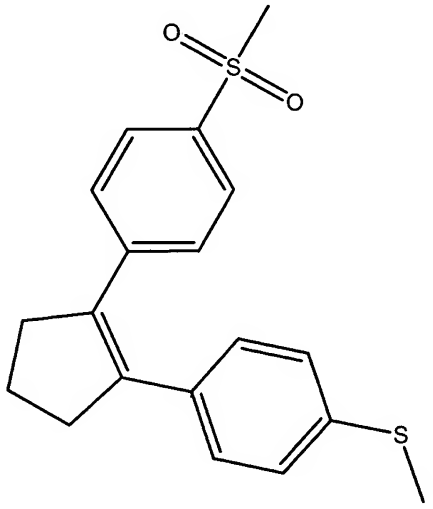
Compound	Name and/or Structure (COX 2 Inhibitor)
B-166	 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;
B-167	 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

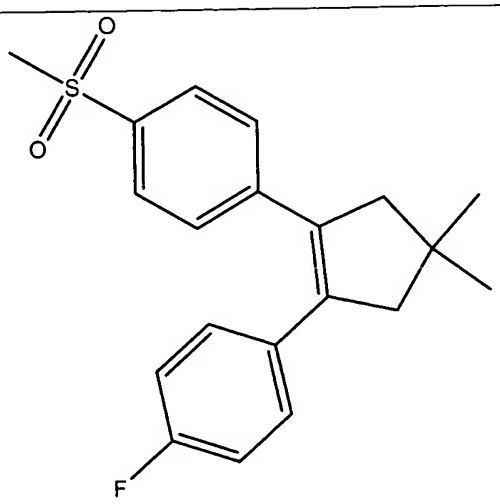
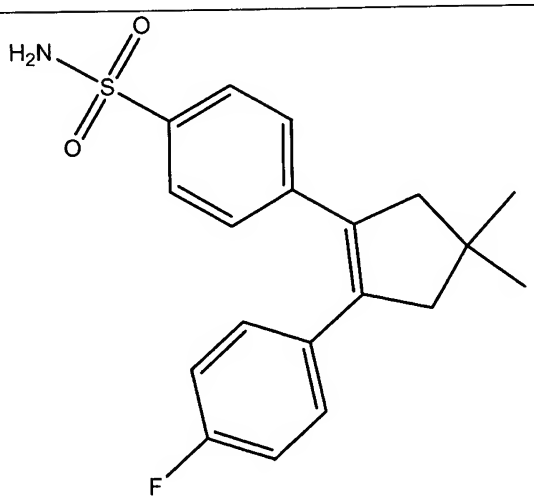
Compound	Name and/or Structure (COX 2 Inhibitor)
B-168	 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;
B-169	 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

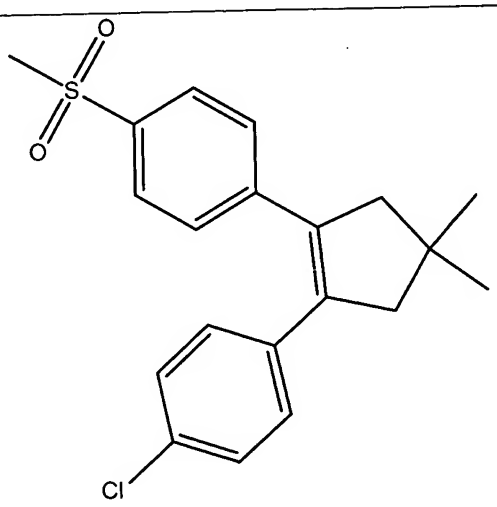
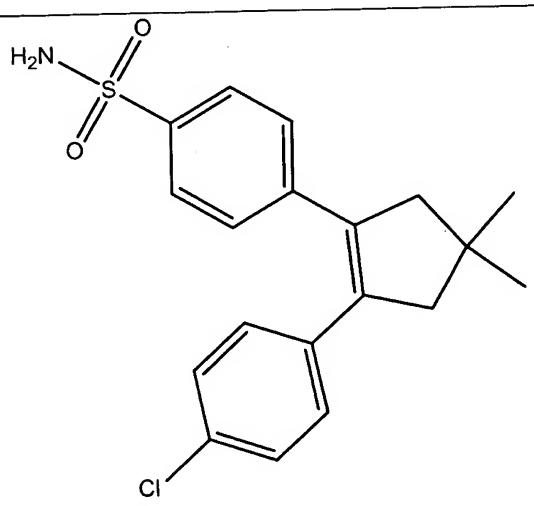
Compound	Name and/or Structure (COX 2 Inhibitor)
B-170	 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
B-171	 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

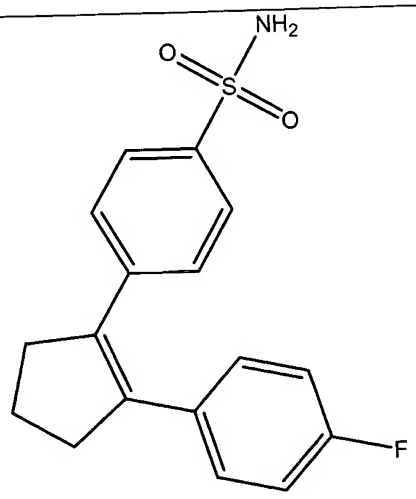
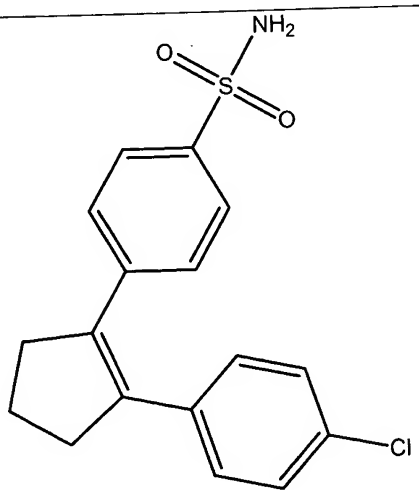
Compound	Name and/or Structure (COX 2 Inhibitor)
B-172	 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-173	 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

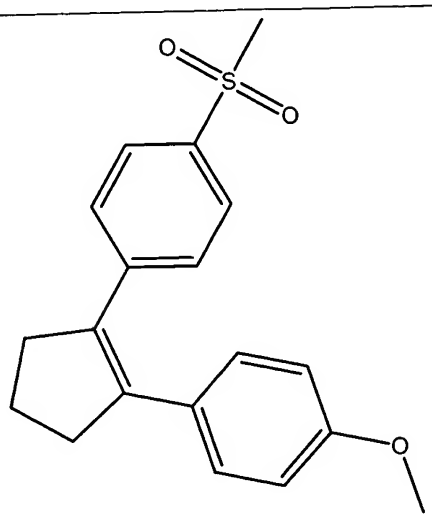
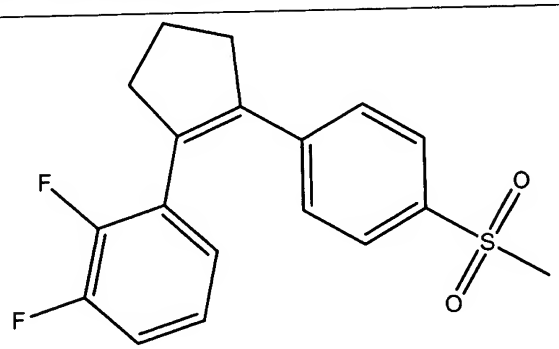
Compound	Name and/or Structure (COX 2 Inhibitor)
B-174	 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-175	 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

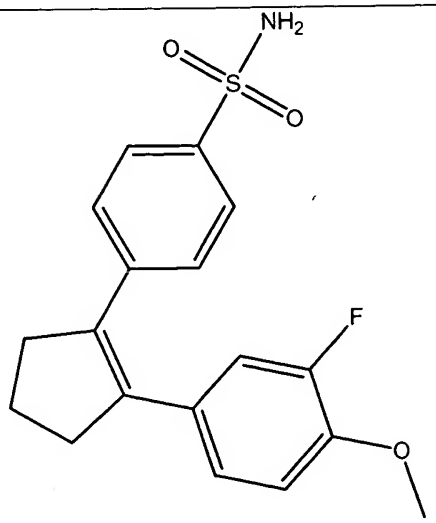
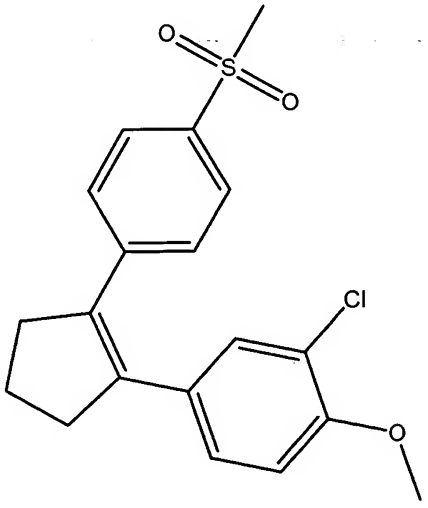
Compound	Name and/or Structure (COX 2 Inhibitor)
B-176	 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-177	 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

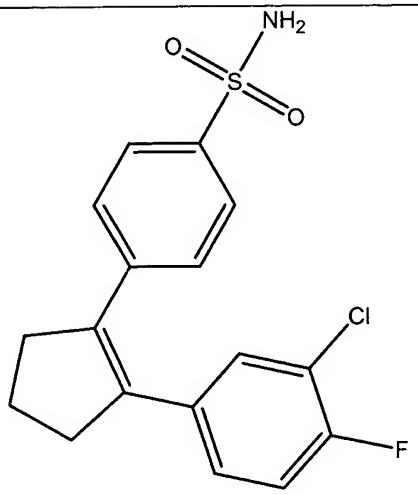
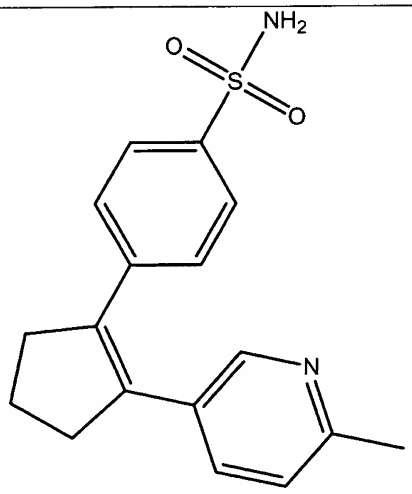
Compound	Name and/or Structure (COX 2 Inhibitor)
B-178	 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-179	 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

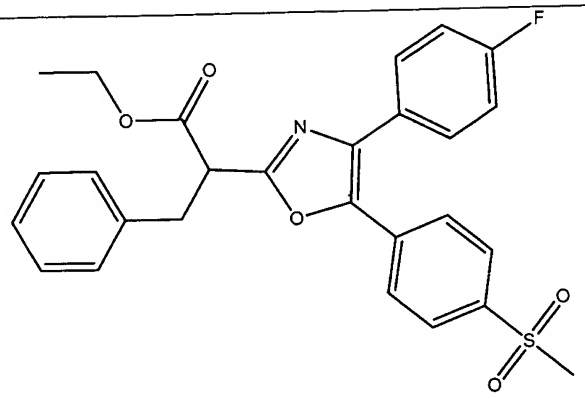
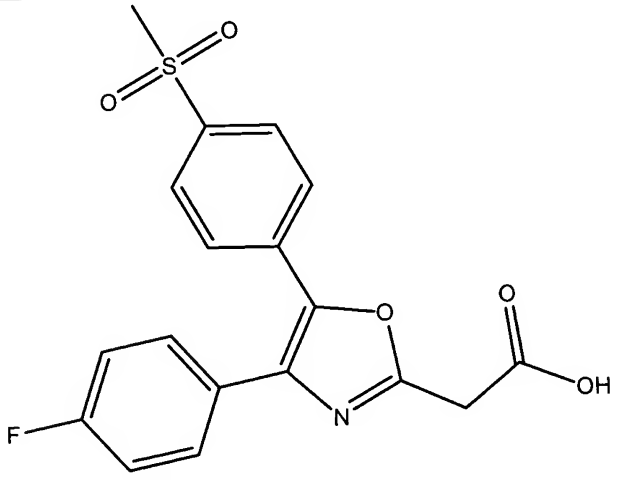
Compound	Name and/or Structure (COX 2 Inhibitor)
B-180	 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-181	 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

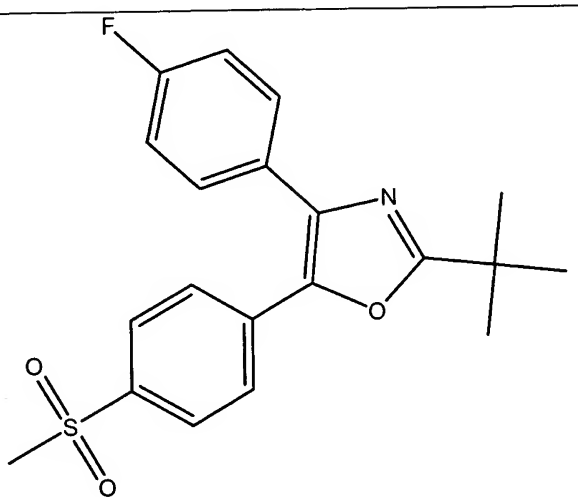
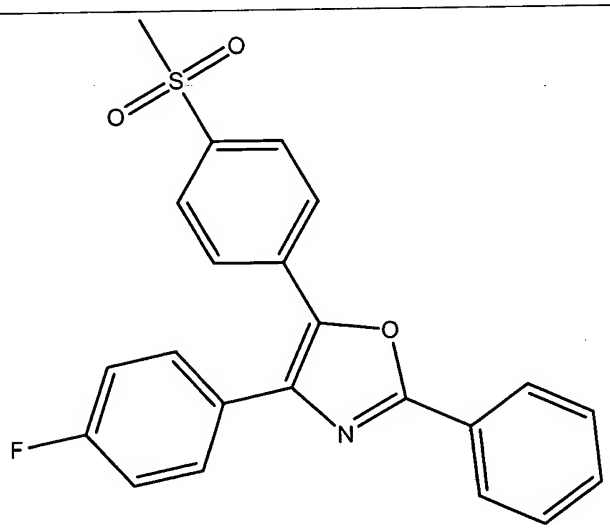
Compound	Name and/or Structure (COX 2 Inhibitor)
B-182	 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
B-183	 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;

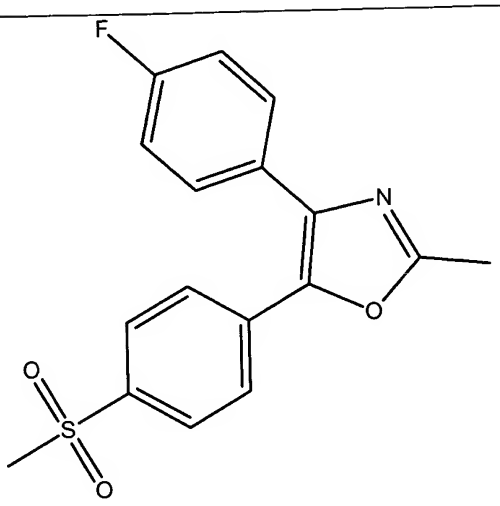
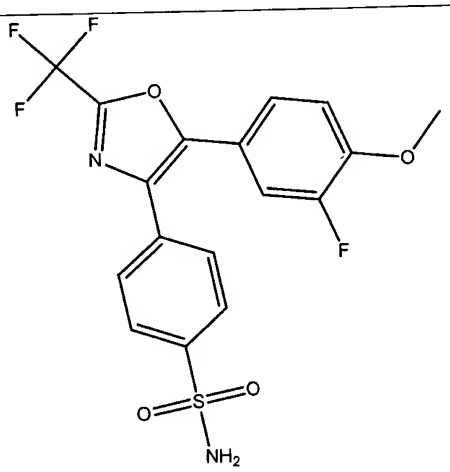
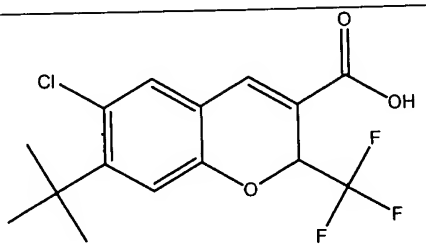
Compound	Name and/or Structure (COX 2 Inhibitor)
B-184	 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;
B-185	 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

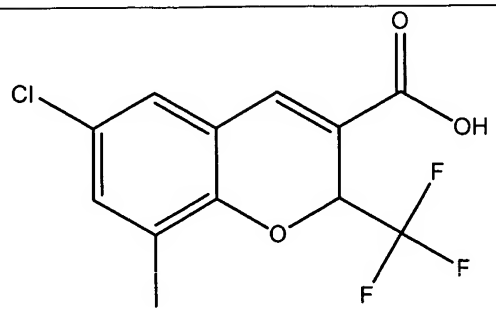
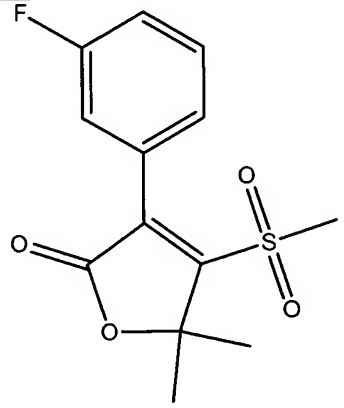
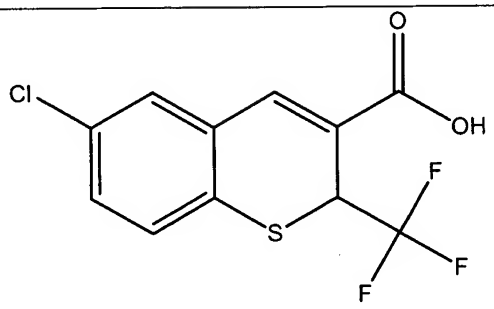
Compound	Name and/or Structure (COX 2 Inhibitor)
B-186	 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;
B-187	 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

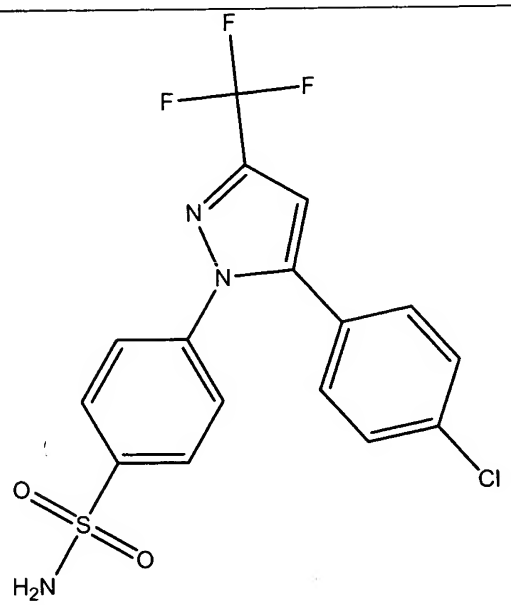
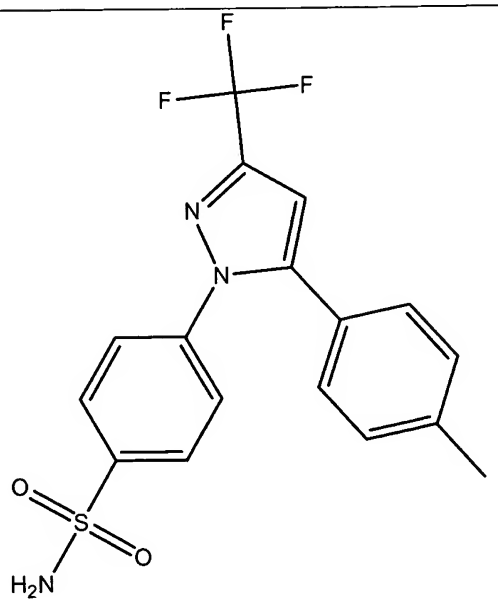
Compound	Name and/or Structure (COX 2 Inhibitor)
B-188	 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;
B-189	 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;

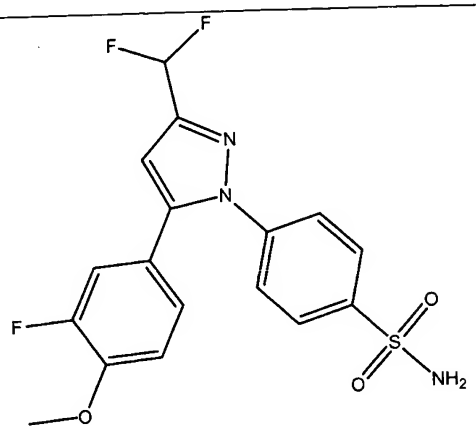
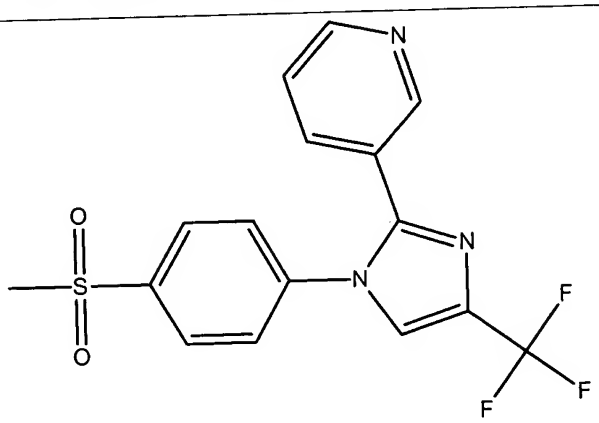
Compound	Name and/or Structure (COX 2 Inhibitor)
B-190	 ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;
B-191	 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;

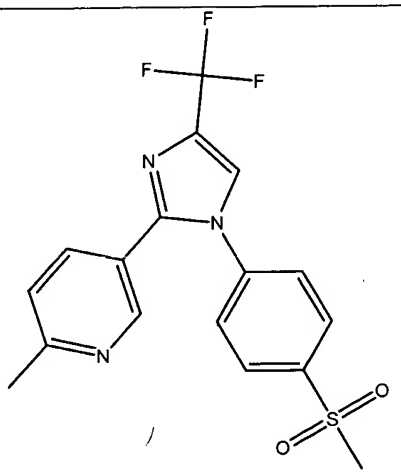
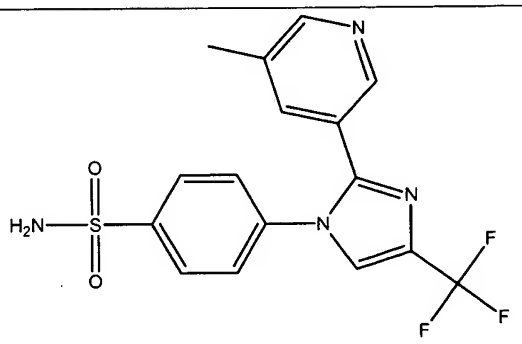
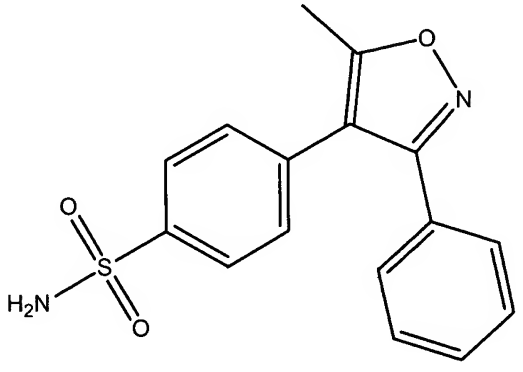
Compound	Name and/or Structure (COX 2 Inhibitor)
B-192	 2-(tert-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;
B-193	 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

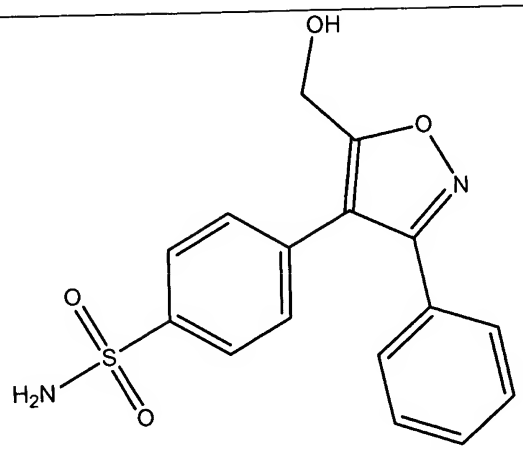
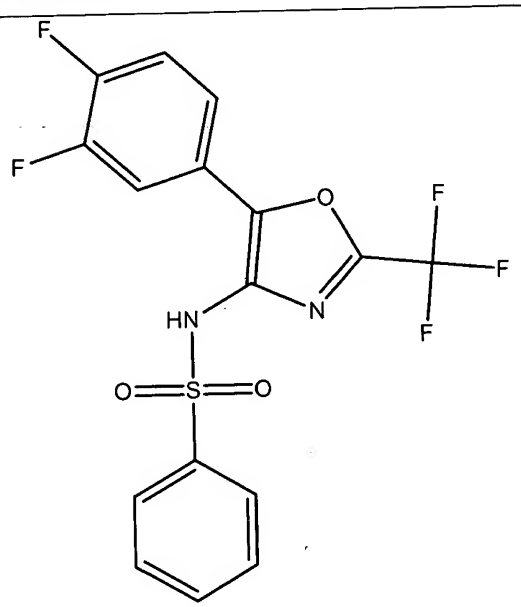
Compound	Name and/or Structure (COX 2 Inhibitor)
B-194	 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole;
B-195	 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;
B-196	 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

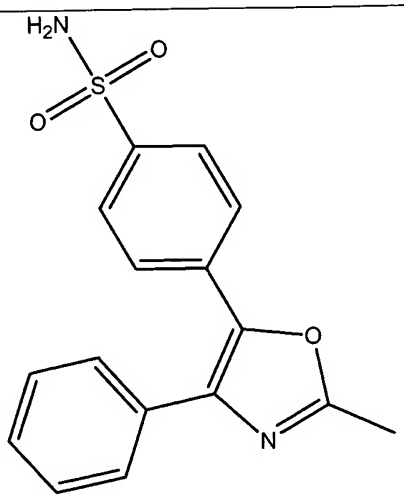
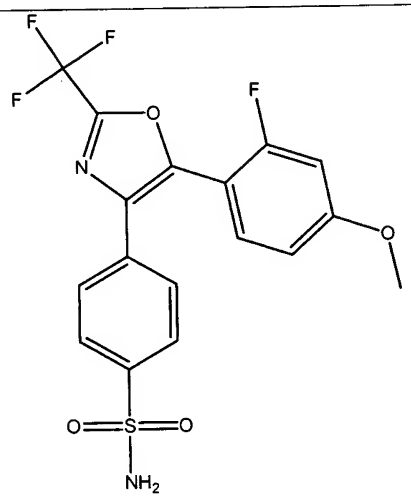
Compound	Name and/or Structure (COX 2 Inhibitor)
B-197	 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;
B-198	 5,5-dimethyl-3-(3-fluorophenyl)-4-methylsulfonyl-2(5H)-furanone;
B-199	 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

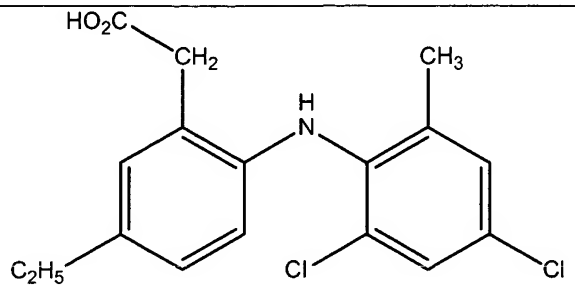
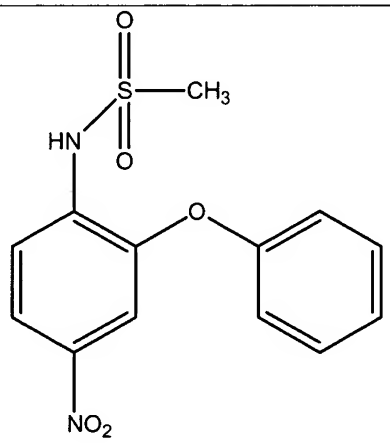
Compound	Name and/or Structure (COX 2 Inhibitor)
B-200	 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-201	 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

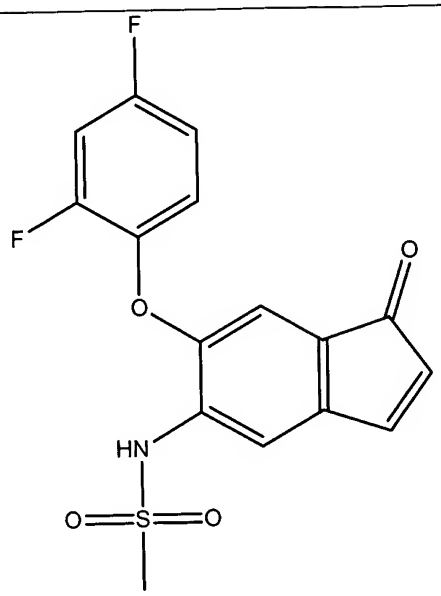
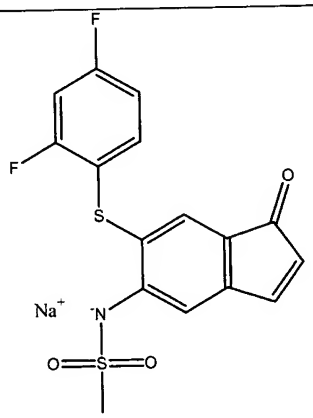
Compound	Name and/or Structure (COX 2 Inhibitor)
B-202	 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;
B-203	 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

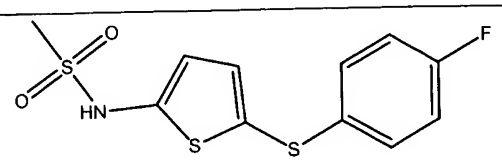
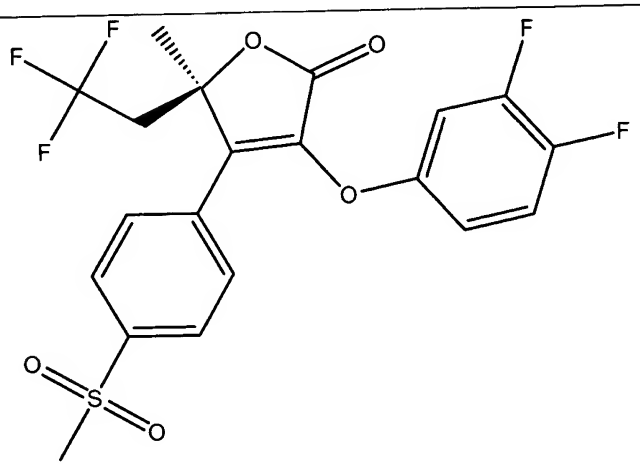
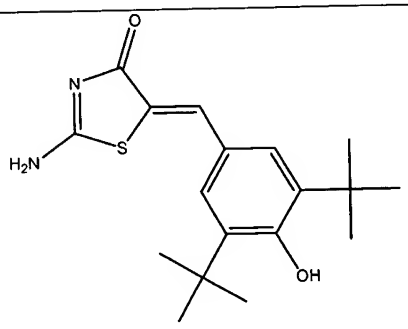
Compound	Name and/or Structure (COX 2 Inhibitor)
B-204	 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;
B-205	 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;
B-206	 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

Compound	Name and/or Structure (COX 2 Inhibitor)
B-207	 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;
B-208	 [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

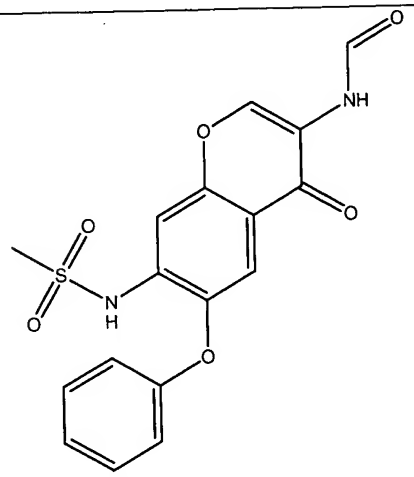
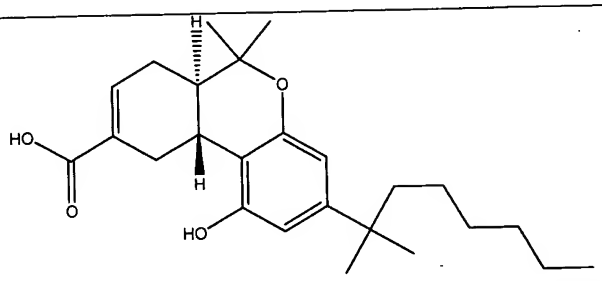
Compound	Name and/or Structure (COX 2 Inhibitor)
B-209	 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide;
B-210	 4-[5-(2-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide;

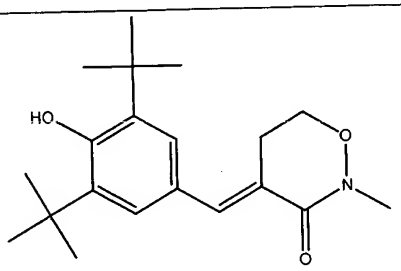
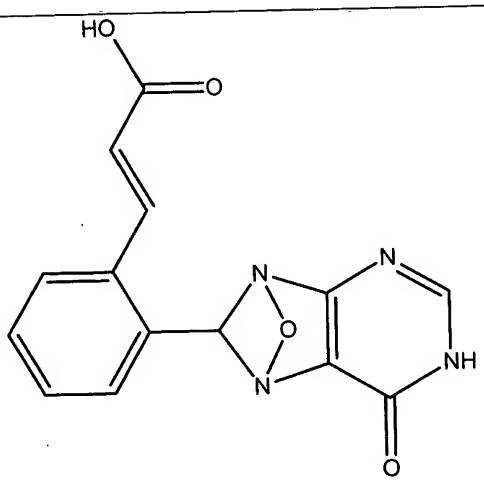
Compound	Name and/or Structure (COX 2 Inhibitor)
B-211	 [2-(2,4-dichloro-6-methyl-phenylamino)-5-ethyl-phenyl]-acetic acid or COX 189 or Lumiracoxib
B-212	 *N*-(4-Nitro-2-phenoxy-phenyl)-methanesulfonamide or Nimesulide

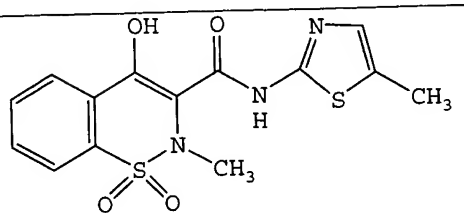
Compound	Name and/or Structure (COX 2 Inhibitor)
B-213	 N-[6-(2,4-Difluoro-phenoxy)-1-oxo-inden-5-yl]-methanesulfonamide or Flosulide
B-214	 *N*-[6-(2,4-Difluoro-phenylsulfanyl)-1-oxo-1*H*-inden-5-yl]-methanesulfonamide, soldium salt, or L-745337

Compound	Name and/or Structure (COX 2 Inhibitor)
B-215	 N-[5-(4-fluoro-phenylsulfanyl)-thiophen-2-yl]-methanesulfonamide or RWJ-63556
B-216	 3-(3,4-Difluoro-phenoxy)-4-(4-methanesulfonyl-phenyl)-5-methyl -5-(2,2,2-trifluoro-ethyl)-5*H*-furan-2-one or L-784512
B-217	 (5Z)-2-amino-5-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]-4(5H)-thiazolone or Darbufelone

Compound	Name and/or Structure (COX 2 Inhibitor)
B-218	CS-502
B-219	LAS-34475
B-220	LAS-34555
B-221	S-33516
B-222	SD-8381
B-223	L-783003

Compound	Name and/or Structure (COX 2 Inhibitor)
B-224	 N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]-methanesulfonamide or T614
B-225	D-1367
B-226	L-748731
B-227	 (6aR,10aR)-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-carboxylic acid or CT 3

Compound	Name and/or Structure (COX 2 Inhibitor)
B-228	CGP-28238
B-229	 4-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene]dihydro-2-methyl-2H-1,2-oxazin-3(4H)-one or BF-389
B-230	GR-253035
B-231	 2-(6-dioxo-9H-purin-8-yl)cinnamic acid
B-232	S-2474

Compound	Name and/or Structure (COX 2 Inhibitor)
B-233	 meloxicam

The cyclooxygenase -2 selective inhibitors described above may be referred to herein collectively as COX-2 selective inhibitors, or cyclooxygenase-2 selective inhibitors.

Cyclooxygenase-2 selective inhibitors that are useful in the present invention can be supplied by any source as long as the cyclooxygenase-2-selective inhibitor is pharmaceutically acceptable. Cyclooxygenase-2-selective inhibitors can be isolated and purified from natural sources or can be synthesized. Cyclooxygenase-2-selective inhibitors should be of a quality and purity that is conventional in the trade for use in pharmaceutical products.

In the present method, a subject in need of prevention or treatment of a CNS disorder and/or pain (*e.g.*, neuropathic pain) and inflammation or an inflammation-associated disorder is treated with an amount of duloxetine, venlafaxine or atomoxetine (or combinations thereof) and an amount of a COX-2 selective inhibitor, where the amount of the duloxetine, venlafaxine or atomoxetine (or combinations thereof), when administered with an amount of the COX-2 selective inhibitor, together provide a dosage or amount in combination that is sufficient to constitute a CNS disorder and/or pain (*e.g.*, neuropathic pain) and inflammation suppressing treatment, prevention, or inhibition effective amount.

As used herein, an "effective amount" means the dose or effective amount to be administered to a patient and the frequency of administration to the subject which is sufficient to obtain a therapeutic effect as readily determined by one or ordinary skill in the art, by the use of known techniques and by observing results obtained under analogous circumstances. The dose or effective amount to be administered to a patient and the frequency of administration to the subject can be readily determined by one of ordinary skill in the art by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including but not limited to, the potency and duration of action of the compounds used; the nature and severity of the illness to be treated as well as on the sex, age, weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances.

The phrase "therapeutically-effective" indicates the capability of an agent to prevent, or improve the severity of, the disorder, while avoiding adverse side effects typically associated with alternative therapies.

Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711.

In the present method, the amount of venlafaxine that is used in the novel method of treatment preferably ranges from about 0.01 to about 10 milligrams per day per kilogram of body weight of the subject (mg/day·kg), more preferably from about 0.1 to about 5 mg/day·kg, more preferably from about 0.2 mg/day kg to about 4 mg/day kg and yet even more preferably from about 0.5 to about 2 mg/day·kg. The absolute daily amount of venlafaxine administered is preferably from about 37.5 mg/day to about 375 mg/day, more preferably from about 75 mg/day to about 225

mg/day, even more preferably from about 75 mg/day to about 150 mg/day, and still more preferably from about 80 mg/day to about 120 mg/day.

In the present method, the amount of atomoxetine that is used in the novel method of treatment preferably ranges from about 0.01 to about 10 milligrams per day per kilogram of body weight of the subject (mg/day·kg), more preferably from about 0.4 to about 2.0 mg/day·kg, even more preferably from about 0.5 to about 1.9 mg/day·kg, and still more preferably from about 1.2 to about 1.8 mg/day·kg. The absolute daily amount of atomoxetine administered is preferably from about 5 mg/day to about 500 mg/day, more preferably from about 50 mg/day to about 200 mg/day, and even more preferably from about 75 mg/day to about 150 mg/day.

In the present method, the amount of duloxetine that is used in the novel method of treatment preferably ranges from about 0.01 to about 10 milligrams per day per kilogram of body weight of the subject (mg/day·kg), more preferably from about 0.4 to about 2.0 mg/day·kg, even more preferably from about 0.5 to about 1.9 mg/day·kg, and still more preferably from about 1.2 to about 1.8 mg/day·kg. The absolute daily amount of duloxetine administered is preferably from about 5 mg/day to about 500 mg/day, more preferably from about 50 mg/day to about 200 mg/day, and even more preferably from about 75 mg/day to about 150 mg/day.

The amount of COX-2 selective inhibitor that is used in the subject method may be an amount that, when administered in combination with the duloxetine, venlafaxine or atomoxetine, is sufficient to constitute a CNS disorder and/or pain and inflammation suppressing treatment, prevention, or inhibition effective amount. In the present method, the amount of COX-2 selective inhibitor that is used in the novel method of treatment preferably ranges from about 0.01 to about 100 milligrams per day per kilogram of body weight of the subject (mg/day·kg), more

preferably from about 1 to about 50 mg/day·kg, even more preferably from about 1 to about 20 mg/day·kg.

When the COX 2 selective inhibitor comprises rofecoxib, it is preferred that the amount used is within a range from about 0.15 to about 1.0 mg/day·kg, and even more preferably from about 0.18 to about 0.4 mg/day·kg. When the COX 2 selective inhibitor comprises etoricoxib, it is preferred that the amount used is within a range from about 0.5 to about 5 mg/day·kg, and even more preferably from about 0.8 to about 4 mg/day·kg. When the COX 2 selective inhibitor comprises celecoxib, it is preferred that the amount used is within a range from about 1 to about 20 mg/day·kg, even more preferably from about 1.4 to about 8.6 mg/day·kg, and yet more preferably from about 2 to about 3 mg/day·kg. When the COX 2 selective inhibitor comprises valdecoxib, it is preferred that the amount used is within a range from about 0.1 to about 5 mg/day·kg, and even more preferably from about 0.8 to about 4 mg/day·kg. When the COX 2 selective inhibitor comprises parecoxib, it is preferred that the amount used is within a range from about 0.1 to about 5 mg/day·kg, and even more preferably from about 1 to about 3 mg/day·kg.

In terms of absolute daily dosages, when the COX 2 selective inhibitor comprises rofecoxib, it is preferred that the amount used is from about 10 to about 75 mg/day, more preferably from about 12.5 to about 50 mg/day. When the COX 2 selective inhibitor comprises etoricoxib, it is preferred that the amount used is from about 50 to about 100 mg/day, more preferably from about 60 to about 90 mg/day. When the COX 2 selective inhibitor comprises celecoxib, it is preferred that the amount used is from about 100 to about 1000 mg/day, more preferably from about 200 to about 800 mg/day. When the COX 2 selective inhibitor comprises valdecoxib, it is preferred that the amount used is from about 5 to about 100 mg/day, more preferably from about 10 to about 60 mg/day. When the COX 2 selective inhibitor comprises parecoxib, it is preferred that the

amount used is within a range from about 10 to about 100 mg/day, more preferably from about 20 to about 80 mg/day.

In the present method, and in the subject compositions, duloxetine, venlafaxine and/or atomoxetine is administered with, or is combined with, a COX-2 selective inhibitor. It is preferred that the weight ratio of the amount of COX-2 selective inhibitor to the amount of duloxetine, venlafaxine and/or atomoxetine that is administered to the subject is within a range from about 0.1:1 to about 10:1, more preferably in a range from about 0.2:1 to about 5:1, even more preferably in a range from about 0.4:1 to about 2:1.

The combination of duloxetine venlafaxine and/or atomoxetine and a COX-2 selective inhibitor can be supplied in the form of a novel therapeutic composition that is believed to be within the scope of the present invention. The relative amounts of each component in the therapeutic composition may be varied and may be as described just above. The duloxetine, venlafaxine and/or atomoxetine and COX-2 selective inhibitor that are described above can be provided in the therapeutic composition so that the preferred amounts of each of the two components are supplied by a single dosage, a single capsule for example, or, by up to four, or more, single dosage forms.

When the novel combination is supplied along with a pharmaceutically acceptable carrier, a pharmaceutical composition is formed. A pharmaceutical composition of the present invention is directed to a composition suitable for the prevention or treatment of a CNS disorder and/or pain and inflammation or an inflammation-associated disorder. The pharmaceutical composition comprises a pharmaceutically acceptable carrier and a combination selected from duloxetine, venlafaxine and/or atomoxetine and cyclooxygenase-2 selective inhibitors. Pharmaceutically acceptable carriers include, but are not limited to, physiological saline, Ringer's, phosphate solution or buffer, buffered saline, and other carriers

known in the art. Pharmaceutical compositions may also include stabilizers, anti-oxidants, colorants, and diluents. Pharmaceutically acceptable carriers and additives are chosen such that side effects from the pharmaceutical compounds are minimized and the performance of the compounds is not canceled or inhibited to such an extent that treatment is ineffective.

The term "pharmacologically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by a researcher or clinician. This amount can be a therapeutically effective amount.

The term "pharmaceutically acceptable" is used herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to, appropriate alkali metal salts, alkaline earth metal salts and other physiological acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated tertiary amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include, without limitation, hydrochloric acid, hydroiodic acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

Also included in the combination of the invention are the isomeric forms and tautomers and the pharmaceutically-acceptable salts of duloxetine, venlafaxine or atomoxetine and cyclooxygenase-2 selective inhibitors. Illustrative pharmaceutically acceptable salts are prepared from formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, stearic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesulfonic, sulfanilic, cyclohexylaminosulfonic, algenic, β-hydroxybutyric, galactaric and galacturonic acids.

Suitable pharmaceutically-acceptable base addition salts of compounds of the present invention include metallic ion salts and organic ion salts. More preferred metallic ion salts include, but are not limited to, appropriate alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts and other physiological acceptable metal ions. Such salts can be made from the ions of aluminum, calcium, lithium, magnesium, potassium, sodium and zinc. Preferred organic salts can be made from tertiary amines and quaternary ammonium salts, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of the above salts can be prepared by those skilled in the art by conventional means from the corresponding compound of the present invention.

The method and combination of the present invention are useful for, but not limited to, the treatment, prevention, or inhibition of a CNS disorder and/or pain and inflammation in a subject, and for treatment of inflammation-associated disorders, such as for use as an analgesic in the treatment of neuropathic pain.

Combinations of the invention would also be useful to treat gastrointestinal conditions such as inflammatory bowel disease, gastric ulcer, gastric varices, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis and for the prevention or treatment of cancer, such as colorectal cancer, and the pain associated with cancer. Combinations of the invention would be useful in treating inflammation in diseases and conditions such as herpes infections (*e.g.*, herpes simplex), HIV, pulmonary edema, kidney stones, minor injuries, wound healing, vaginitis, candidiasis, lumbar spondylarthrosis, vascular diseases, migraine headaches, sinus headaches, tension headaches, dental pain, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, diabetes mellitus (type 1 and type 2), myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like.

Compositions having the novel combination would also be useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, conjunctivitis, uveitis, ocular photophobia, and of acute injury to the eye tissue. The compositions would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The compositions would also be useful for the treatment of certain central nervous system disorders such as cortical dementias including Alzheimer's disease. The combinations of the invention are also useful as anti-inflammatory agents, such as for the treatment of arthritis.

Inflammation-associated disorders in addition to some of those mentioned above that would be useful using the combination of the present invention include actinomycosis, acute appendicitis, acute cholecystitis, acute hemorrhagic encephalitis, acute hepatitis, acute myocardial infarction, acute pancreatitis, adenitis, amebiasis, amebic colitis, anal fissures, ankylosing spondylitis, aphthous stomatitis, aphthous ulcers,

appendiceal abscess, arachnoiditis, arteritis, asthma, atherosclerosis, atopic dermatitis, B virus myelitis, "backwash" ileitis of ulcerative colitis, bacterial endocarditis, berylliosis, blastomyces dermatitidis, blepharitis, brain abscess, bronchiectasis, bronchiolitis, brucellosis, bursitis, carcinoma of the bile ducts, cat-scratch fever, cavernous sinus thrombosis, cecal diverticulitis, cellulitis, cerebral epidural abcess, cholelithiasis, chondritis, choreoretinitis, chronic active hepatitis, coccidioides immitis, cortical thrombophlebitis, cryptococcus neoformans, dacryocystitis, dermatomyositis, diabetic neuropathy, encephalitis, encephalomyelitis, endometritis, endophthalmitis, eosinophilic gastroenteritis, epicondylitis, epiglottitis, erythema multiforme, erythema nodosum, external ear inflammatory disease, fasciitis, fibromyalgia, fistulas, folliculitis, gliosis, glomerulonephritis, gonococcal infection, gout, granulomatous colitis, hemorrhoids, hepatitis, ileal carcinoid, ileitis, ileocecal tuberculosis, ileocolitis, ileojejunitis, iliofemoral venous thrombosis, incarcerated hernia, infarction of the colon, interstitial keratitis, intestinal obstruction, iritis, ischemia, ischemic colitis, labyrinthitis, lateral sinus thrombosis, leprosy, low back pain, lymphadenitis, lymphangitis, lymphogranuloma inguinale, lymphosarcoma, mastoiditis, mesenteric thrombosis, metastatic melanocarcinoma, myositis, myringitis, nephritis, neuritis, neuronitis, neurosyphilis, nodular lymphoid hyperplasia, osteoarthritis, osteomyelitis, otitis, ovarian carcinoma, panencephalitis, papillitis, parenchymatous, pelvic inflammatory disease, perforated ulcer, perianal abscess, pericarditis, pericholangitis, periodontitis, peritonitis, pharyngitis, pleuritis, pneumonia, pneumonitis, poliomyelitis, postherpetic neuralgia, prostatitis, pseudomembranous enterocolitis, pseudopolyps, psoriasis, pulmonary infarction, pulmonary inflammation, pulpitis, pyelonephritis, pylephlebitis, pyoderma gangrenosum, rabies, radiation colitis, radiation enteritis, rectal prolapse, regional enteritis, renal amyloidosis, rheumatoid arthritis, rhinitis, rickettsiae, sacroiliitis, salpingitis, scleritis, sclerosing cholangitis, septic thrombophlebitis, shigellosis, shingles,

sinusitis, spinal epidural abscess, splenitis, subdural empyema, syphilitic meningovascular syphilis, tabes dorsalis, tendonitis, tenosynovitis, tinnitis, tonsillitis, toxic megacolon, transverse myelitis, trigeminal neuralgia, tuberculosis enteritis, typhoid fever, ulcerative proctitis, ureteritis, vascular necrosis, vasculitis, ventricular empyema, vestibulitis, and Zollinger-Ellison syndrome.

As used herein, the terms "pain, inflammation or inflammation-associated disorder", and "cyclooxygenase-2 mediated disorder" are meant to include, without limitation, each of the symptoms or diseases that is mentioned above.

The present method includes the treatment and/or prevention of a cyclooxygenase-2 mediated disorder in a subject, where the method comprises treating the subject having or susceptible to the disorder with a therapeutically-effective amount of a combination of duloxetine, venlafaxine or atomoxetine and a compound or salt of any of the cyclooxygenase-2 selective inhibitors that are described in this specification.

The terms "treating" or "to treat" means to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms. The term "treatment" includes alleviation, elimination of causation of or prevention of pain and/or inflammation associated with, but not limited to, any of the diseases or disorders described above. Besides being useful for human treatment, these combinations are also useful for treatment of mammals, including horses, dogs, cats, rats, mice, sheep, pigs, other domestic and veterinary animals, etc.

The term "subject" for purposes of treatment includes any human or animal subject who is in need of the prevention of, or who has pain, inflammation and/or any one of the known inflammation-associated disorders. The subject is typically a human subject.

For methods of prevention, the subject is any human or animal subject, and preferably is a subject that is in need of treatment, prevention, or inhibition a CNS and/or pain and inflammation or an inflammation-associated disorder. The subject may be a human subject who is at risk for pain and/or inflammation, or for obtaining an inflammation-associated disorder, such as those described above. The subject may be at risk due to genetic predisposition, sedentary lifestyle, diet, exposure to disorder-causing agents, exposure to pathogenic agents and the like.

The pharmaceutical compositions may be administered enterally and parenterally. Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art. Enteral administration includes solution, tablets, sustained release capsules, enteric coated capsules, and syrups. When administered, the pharmaceutical composition may be at or near body temperature.

The phrases "combination therapy", "co-administration", "administration with", or "co-therapy", in defining the use of a cyclooxygenase-2 inhibitor agent and duloxetine, venlafaxine or atomoxetine, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule or dosage device having a fixed ratio of these active agents or in multiple, separate capsules or dosage devices for each agent, where the separate capsules or dosage devices can be taken together contemporaneously, or taken within a period of time sufficient to receive a beneficial effect from both of the constituent agents of the combination.

The phrase "therapeutically-effective" and "effective for the treatment, prevention, or inhibition", are is intended to qualify the amount

of each agent for use in the combination therapy which will achieve the goal of improvement in inflammation severity and the frequency of incidence over treatment of each agent by itself, while avoiding adverse side effects typically associated with alternative therapies.

Although the combination of the present invention may include administration of a duloxetine, venlafaxine or atomoxetine component and a cyclooxygenase-2 selective inhibitor component within an effective time of each respective component, it is preferable to administer both respective components contemporaneously, and more preferable to administer both respective components in a single delivery dose.

In particular, the combinations of the present invention can be administered orally, for example, as tablets, coated tablets, dragees, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay

material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are present as such, or mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions can be produced that contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in an omega-3 fatty acid, a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid

paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Syrups and elixirs containing the novel combination may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The subject combinations can also be administered parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or olagenous suspensions. Such suspensions may be formulated according to the known art using those suitable dispersing of wetting agents and suspending agents which have been mentioned above, or other acceptable agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including

synthetic mono- or diglycerides. In addition, n-3 polyunsaturated fatty acids may find use in the preparation of injectables.

The subject combination can also be administered by inhalation, in the form of aerosols or solutions for nebulizers, or rectally, in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and poly-ethylene glycols.

The novel compositions can also be administered topically, in the form of creams, ointments, jellies, collyriums, solutions or suspensions. Of course, the compositions of the present invention can be administered by routes of administration other than topical administration.

Daily dosages can vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage has been described above, although the limits that were identified as being preferred may be exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages.

Various delivery systems include capsules, tablets, and gelatin capsules, for example.

The present invention further comprises kits that are suitable for use in performing the methods of treatment, prevention or inhibition described above. In one embodiment, the kit contains a first dosage form comprising duloxetine, venlafaxine or atomoxetine in one or more of the forms identified above and a second dosage form comprising one or more of the cyclooxygenase-2 selective inhibitors or prodrugs thereof identified above, in quantities sufficient to carry out the methods of the present invention. Preferably, the first dosage form and the second dosage form together comprise a therapeutically effective amount of the compounds for

the treatment, prevention, or inhibition of pain, inflammation or inflammation-associated disorder.

The following examples describe embodiments of the invention. Other embodiments within the scope of the embodiments herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the embodiments and the examples. In the examples, all percentages are given on a weight basis unless otherwise indicated.

COMPARATIVE EXAMPLE 1

This example shows the preparation of celecoxib.

Step 1: Preparation of 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione.

Following the disclosure provided in U.S. Patent No. 5,760,068, 4'-Methylacetophenone (5.26 g, 39.2 mmol) was dissolved in 25 mL of methanol under argon and 12 mL (52.5 mmol) sodium methoxide in methanol (25%) was added. The mixture was stirred for 5 minutes and 5.5 mL (46.2 mmol) ethyl trifluoroacetate was added. After refluxing for 24 hours, the mixture was cooled to room temperature and concentrated. 100 mL 10% HCl was added and the mixture extracted with 4 x 75 mL ethyl acetate. The extracts were dried over $MgSO_4$, filtered and concentrated to afford 8.47 g (94%) of a brown oil which was carried on without further purification.

Step 2: Preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

To the dione from Step 1 (4.14 g, 18.0 mmol) in 75 mL absolute ethanol, 4.26 g (19.0 mmol) 4-sulphonamidophenylhydrazine hydrochloride was added. The reaction was refluxed under argon for 24 hours. After cooling to room temperature and filtering, the reaction mixture was concentrated to afford 6.13 g of an orange solid. The solid was recrystallized from methylene chloride/hexane to give 3.11 g (8.2 mmol, 46%) of the product as a pale yellow solid, having a melting point (mp) of 157°-159°C; and a calculated composition of $C_{17}H_{14}N_3O_2SF_3$: C, 53.54; H, 3.70; N, 11.02. The composition that was found by analysis was: C, 53.17; H, 3.81; N, 10.90.

EXAMPLE 2

This illustrates the production of a composition containing celebrex and duloxetine, venlafaxine or atomoxetine and of pharmaceutical compositions containing the combinations.

A composition of the present invention can be formed by intermixing duloxetine, venlafaxine or atomoxetine and 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (as produced in Comparative Example 1, or as available from Pharmacia Corporation, St. Louis, MO), in a laboratory mill or mixing device suitable for intimate mixing of powders without substantial generation of shear or temperature sufficient to degrade either of the two compounds. After mixing, the combination of celecoxib and duloxetine, venlafaxine or atomoxetine form a composition that is sufficient for the production of about 1000 human single dose units.

If desirable, a solid carrier and other materials may be intermixed with the therapeutic composition to form a pharmaceutical composition and the resulting pharmaceutical composition may be formed into capsules for human consumption, for example, by conventional capsule-forming equipment, where each capsule contains specified amounts of duloxetine, venlafaxine or atomoxetine and celecoxib. Alternatively, the duloxetine, venlafaxine or atomoxetine and the celecoxib may be dissolved into a liquid carrier, such as, for example, normal saline solution, to form a pharmaceutical composition suitable for human consumption. A single dosage of the liquid pharmaceutical composition for human use would be a volume sufficient to provide specific amounts of duloxetine, venlafaxine or atomoxetine and celecoxib in a therapeutically effective formulation.

Therapeutic and pharmaceutical compositions comprising a combination of any of the cyclooxygenase-2-selective inhibitors and duloxetine, venlafaxine or atomoxetine that are described above can be formed by similar methods.

EXAMPLE 3

This illustrates the evaluation of the biological efficacy of a composition of duloxetine, venlafaxine or atomoxetine and celecoxib.

A composition containing duloxetine, venlafaxine or atomoxetine and celecoxib is prepared as described in Example 2. The biological efficacy of the composition is determined by a rat carrageenan foot pad edema test and by a rat carrageenan-induced analgesia test.

Rat Carrageenan Foot Pad Edema Test:

The carrageenan foot edema test is performed with materials, reagents and procedures essentially as described by Winter, *et al.*, (*Proc. Soc. Exp. Biol. Med., 111*, 544 (1962)). Male Sprague-Dawley rats are selected in each group so that the average body weight is as close as possible. Rats are fasted with free access to water for over sixteen hours prior to the test. The rats are dosed orally (1 mL) with compounds suspended in a carrier vehicle containing 0.5% methylcellulose and 0.025% surfactant, or with only the carrier vehicle alone. One hour later, a subplantar injection of 0.1 mL of 1% solution of carrageenan/sterile 0.9% saline is administered to one foot and the volume of the injected foot is measured with a displacement plethysmometer connected to a pressure transducer with a digital indicator. Three hours after the injection of the carrageenan, the volume of the foot is again measured. The average foot swelling in a group of drug-treated animals is compared with that of a group of placebo-treated animals and the percentage inhibition of edema is determined (Otterness and Bliven, Laboratory Models for Testing NSAIDS, in *Non-steroidal Anti-Inflammatory Drugs*, (J. Lombardino, ed. 1985)). The percent inhibition shows the percent decrease from control paw volume determined in this procedure. The data are expected to show that the combination of duloxetine, venlafaxine or atomoxetine and celecoxib provided effective anti-inflammatory activity.

Rat Carrageenan-induced Analgesia Test:

The analgesia test using rat carrageenan is performed with materials, reagents and procedures essentially as described by Hargreaves, *et al.*, (*Pain*, 32, 77 (1988)). Male Sprague-Dawley rats are

treated as previously described for the Carrageenan Foot Pad Edema test. Three hours after the injection of the carrageenan, the rats are placed in a special PLEXIGLAS® container with a transparent floor having a high intensity lamp as a radiant heat source, positionable under the floor. After an initial twenty-minute period, thermal stimulation is begun on either the injected foot or on the contralateral uninjected foot. A photoelectric cell will turn off the lamp and timer when the light is interrupted by paw withdrawal. The time until the rat withdraws its foot is then measured. The withdrawal latency in seconds is determined for the control and drug-treated groups, and percent inhibition of the hyperalgesic foot withdrawal is determined. Results are expected to show that combination of duloxetine, venlafaxine or atomoxetine and celecoxib provided effective analgesic activity.

EXAMPLE 4

This illustrates how to determine the biological efficacy of a composition of duloxetine, venlafaxine or atomoxetine and celecoxib for the treatment of collagen-induced arthritis in mice.

A composition containing duloxetine, venlafaxine or atomoxetine and celecoxib is prepared as described in Example 2. The biological efficacy of the composition is determined by induction and assessment of collagen-induced arthritis in mice.

Arthritis is induced in 8-12 week old male DBA/1 mice by injection of 50 μg of chick-type II collagen (CII) in complete Freunds adjuvant (Sigma) on day 0 at the base of the tail as described in [J. Stuart, *Annual Rev. Immunol., 2*, 199 (1984)]. Compounds are prepared as a suspension in 0.5% methylcellulose (Sigma, St. Louis, Mo.), and 0.025% Tween 20 (Sigma). The cyclooxygenase-2 inhibitor (celecoxib, as described in Comparative Example 1), and duloxetine, venlafaxine or atomoxetine are administered alone or in combination as a therapeutic composition as described in Example 2. The compounds are administered in non-arthritic animals by gavage in a volume of 0.1 ml beginning on day 20 post

collagen injection and continuing daily until final evaluation on day 55. Animals are boosted on day 21 with 50 μg of collagen (CII) in incomplete Freunds adjuvant. The animals are subsequently evaluated several times each week for incidence and severity of arthritis until day 56. Any animal with paw redness or swelling is counted as arthritic. Scoring of severity is carried out using a score of 0-3 for each paw (maximal score of 12/mouse) as described in P. Wooley, *et al., Trans. Proc., 15*, 180 (1983). The animals are measured for incidence of arthritis and severity in the animals where arthritis was observed. The incidence of arthritis is determined at a gross level by observing the swelling or redness in the paw or digits. Severity is measured with the following guidelines. Briefly, animals displaying four normal paws, *i.e.*, no redness or swelling are scored 0. Any redness or swelling of digits or the paw are scored as 1. Gross swelling of the whole paw or deformity is scored as 2. Ankylosis of joints is scored as 3.

Histological Examination of Paws:

In order to verify the gross determination of a non-arthritic animal, a histological examination can be performed. Paws from animals sacrificed at the end of the experiment are removed, fixed and decalcified as previously described [R. Jonsson, *J. Immunol. Methods, 88*, 109 (1986)]. Samples are paraffin embedded, sectioned, and stained with hematoxylin and eosin by standard methods. Stained sections are examined for cellular infiltrates, synovial hyperplasia, and bone and cartilage erosion.

It is expected that results will show that the combination of a cyclooxygenase-2 selective inhibitor with duloxetine, venlafaxine or atomoxetine was an efficacious treatment for collagen-induced arthritis in mice.

All references cited in this specification, including without limitation, all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles,

periodicals, and the like, are hereby incorporated by reference into this specification in their entireties. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

Additional embodiments of the present invention are provided below. In particular, duloxetine, venlafaxine or atomoxetine provided in combination with any one or more of the following COX-2 specific inhibitors as specified in Table 3 below:

Table 3

No.	Name	Compound (or a pharmaceutically acceptable salt or prodrug of the compound)
1.	Duloxetine	In combination with any one of I*, II*, III*, IV*, V*, VI*, VII*, B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B- 11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33, B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100, B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, or B-233.

No.	Name	Compound (or a pharmaceutically acceptable salt or prodrug of the compound)
2.	Venlafaxine	In combination with any one of I*, II*, III*, IV*, V*, VI*, VII*, B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B- 11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33, B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100, B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, or B-233.

No.	Name	Compound (or a pharmaceutically acceptable salt or prodrug of the compound)
3.	Atomoxetine	In combination with any one of I*, II*, III*, IV*, V*, VI*, VII*, B-1, B-2, B-3, B-4, B-5, B-6, B-7, B-8, B-9, B-10, B- 11, B-12, B-13, B-14, B-15, B-16, B-17, B-18, B-19, B-20, B-21, B-22, B-23, B-24, B-25, B-26, B-27, B-28, B-29, B-30, B-31, B-32, B-33, B-34, B-35, B-36, B-37, B-38, B-39, B-40, B-41, B-42, B-43, B-44, B-45, B-46, B-47, B-48, B-49, B-50, B-51, B-52, B-53, B-54, B-55, B-56, B-57, B-58, B-59, B-60, B-61, B-62, B-63, B-64, B-65, B-66, B-67, B-68, B-69, B-70, B-71, B-72, B-73, B-74, B-75, B-76, B-77, B-78, B-79, B-80, B-81, B-82, B-83, B-84, B-85, B-86, B-87, B-88, B-89, B-90, B-91, B-92, B-93, B-94, B-95, B-96, B-97, B-98, B-99, B-100, B-101, B-102, B-103, B-104, B-105, B-106, B-107, B-108, B-109, B-110, B-111, B-112, B-113, B-114, B-115, B-116, B-117, B-118, B-119, B-120, B-121, B-122, B-123, B-124, B-125, B-126, B-127, B-128, B-129, B-130, B-131, B-132, B-133, B-134, B-135, B-136, B-137, B-138, B-139, B-140, B-141, B-142, B-143, B-144, B-145, B-146, B-147, B-148, B-149, B-150, B-151, B-152, B-153, B-154, B-155, B-156, B-157, B-158, B-159, B-160, B-161, B-162, B-163, B-164, B-165, B-166, B-167, B-168, B-169, B-170, B-171, B-172, B-173, B-174, B-175, B-176, B-177, B-178, B-179, B-180, B-181, B-182, B-183, B-184, B-185, B-186, B-187, B-188, B-189, B-190, B-191, B-192, B-193, B-194, B-195, B-196, B-197, B-198, B-199, B-200, B-201, B-202, B-203, B-204, B-205, B-206, B-207, B-208, B-209, B-210, B-211, B-212, B-213, B-214, B-215, B-216, B-217, B-218, B-219, B-220, B-221, B-222, B-223, B-224, B-225, B-226, B-227, B-228, B-229, B-230, B-231, B-232, or B-233.

* The substituents are as previously described in conjunction with Formulas I-VII, respectively.

Exemplary indications that may be treated with the compositions of Table 3 above are indicated in Table 4 below:

Table 4

No.	Exemplary Indication(s) treated with the duloxetine, venlafaxine and/or atomoxetine and a COX 2-specific inhibitor of Table 3
1.	a CNS disorder including but not limited to any of the CNS disorders indicated below
2.	Pain
3.	Inflammation
4.	Neuropathic pain
5.	Cancer
6.	Pain due to arthritis
7.	Acute pain
8.	Chronic pain
9.	Joint pain
10.	Knee pain
11.	Carpal tunnel syndrome associated pain
12.	Pain associated with inflammation
13.	Pain Associated with Carpal Tunnel Syndrome
14.	Pain Associated with Cervical Disk Degenerative Disease
15.	Pain Associate with Lumbar Disk Degenerative Disease
16.	Pain Associated with Occipital Neuralgia
17.	Pain Associated with Cartilage Tears of the Knee, Elbow or Ankle
18.	Pain Associated with Joint Surface Damage of the Knee, Elbow or Ankle

Exemplary CNS disorders include, but are not limited to, Alzheimer's disease (AD), amnesia, amyotrophic lateral sclerosis (ALS), anorexia nervosa, anxiety disorder, anxiety neurosis, ataxia, attention

deficit hyperactivity disorder, autism, autonomic nervous system disease, behavior disorder, bipolar disorder, brain injury, bulimia, catatonia, central nervous system disease, chronic psychiatric indications, chronic urological indications including incontinence (mixed, urge and stress), cognitive disorder, convulsion, cranial neuropathy, cyclothymia or cyclothymic personality, cystocele, delirium, delusional (paranoid) disorders, dementia, depression, diabetic neuropathy, diverticula, dystonia, dystonia, dysuria, eating disorder, encephalitis, epilepsy, extrapyramidal syndrome, feeding disorder, hermaturia, Huntington's disease (HD) or Huntington's choria, hydronephrosis, hydroureter, hypochondriacal neurosis, hypomanic personality, hypoxia, hysteria, hysterical neurosis, manic depression, meningitis, mental deficiency, mental disorder, motor neurone disease, movement disorder, muscular spasm, multiple sclerosis, myalgia, narcissism, nervous system injury, neurodegenerative disease, neurological disease, neurological, mental and cognitive disorder, neuropathy, obsessive/compulsive disorder, obsessive-compulsive neurosis, opiate use disorder, paralysis, Parkinson's disease (PD), passive-aggressive disorder, personality disorder, phobic neurosis, pneumaturia, posttraumatic stress disorder, psychopathy, psychosis, schizophrenia, seizure, senile dementia, sleep disorder, sociopathy, somatization disorder, stupor, substance dependence, tardive dyskinesia, and tinnitus.

The following Tables 5 and 6 list various dosage forms of the composition of the present invention comprising duloxetine, venlafaxine or atomoxetine and a COX-2 specific inhibitor. Note that the dosage forms in Table 5 exclude all dosage forms that may be transdermally applied. By contrast, Table 6 includes such transdermally applied dosage forms.

Table 5

No.	Exemplary Dosage Forms (other than those that are transdermally applied)
1.	Oral dosage forms
2.	Tablet
3.	Slow Release Tablet
4.	Effervescent Tablet
5.	Enteric Coated Tablet
6.	Compressed Tablet
7.	Molded Tablet
8.	Capsule
9.	Slow Release Capsule
10.	Capsule for Use in or with Nebulizer
11.	Gelatin Capsule
12.	Caplet
13.	Troche
14.	Powder
15.	Lozenge
16.	Solution
17.	Suspension
18.	Emulsion
19.	Dispersion
20.	Parenteral Dosage Form
21.	Intramuscular Injection
22.	Intravenous Injection
23.	Inhalant
24.	Aerosol
25.	Nebulizing Liquid
26.	Elixir

No.	Exemplary Dosage Forms (other than those that are transdermally applied)
27.	Collyria
28.	Injection
29.	Pellets
30.	Implants
31.	Otic Solution
32.	Suppository
33.	Syrup
34.	Tincture
35.	Opthalmic Solution
36.	Oral Gel
37.	Oral Paste
38.	Oral Inhalant

Table 6

No.	Exemplary dosage Forms (that are topically applied)
1.	Liquid
2.	Emulsion
3.	Dispersion
4.	Gel
5.	Paste
6.	Cream
7.	Lotion
8.	Extract
9.	Ointment
10.	Patch
11.	Implant
12.	Pellet

13.	Topical Powder
14.	Topical Solution

For a more complete list of dosage forms in addition to those provided in Tables 5 and 6, see Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, PA, Arthur Osol (editor), 16th Edition (1980). Also see each of the later editions of the same (*i.e.*, each later edition to date of Remington's Pharmaceutical Sciences). Also see, The United States Pharmacopeia, 21st Edition, United States Pharmacopeial Convention, Washington, D.C. (1985). Also see each of the later editions of the same (*i.e.*, each later edition to date of The United States Pharmacopeia).